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Transition-Metal-Catalyzed C-C Bonds Formation via Transfer Hydrogenation: From Methodology Development to (+)-SCH 351448 Synthesis

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Transition-Metal-Catalyzed C-C Bonds formation via Transfer Hydrogenation: From Methodology Development to (+)-SCH 351448 Synthesis

by

Gang Wang

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Dedication

To my family

and

my girlfriend – Jingxian Chen

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Transition-Metal-Catalyzed C-C Bonds Formation via Transfer Hydrogenation: From Methodology Development to (+)-SCH 351448 Synthesis

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Supervisor: Michael J. Krische

Redox-triggered carbonyl addition via transfer hydrogenation, which enables direct primary alcohol C-H functionalization to form C-C bond, avoids usage of premetalated reagents or discrete alcohol to aldehyde redox reactions. Moreover, step-economy could be greatly improved by site-selective transformations of polyfunctional molecules due to bypassing the need to install and remove protecting groups. However, the redox site-selective transformations still pose a significant challenge in the area of synthetic organic chemistry. Efforts have been focused on the development of iridium catalyzed transfer hydrogenative coupling reactions of primary alcohols with different allyl donors through carbonyl addition in a site-selective manner as well as ruthenium catalyzed regioselective hydrohydroxyalkylation of primary alcohols with a basic feedstock-styrene. Additionally, studies towards the total synthesis of type I polyketide natural product (+)-SCH 351448 in the most concise route is presented.

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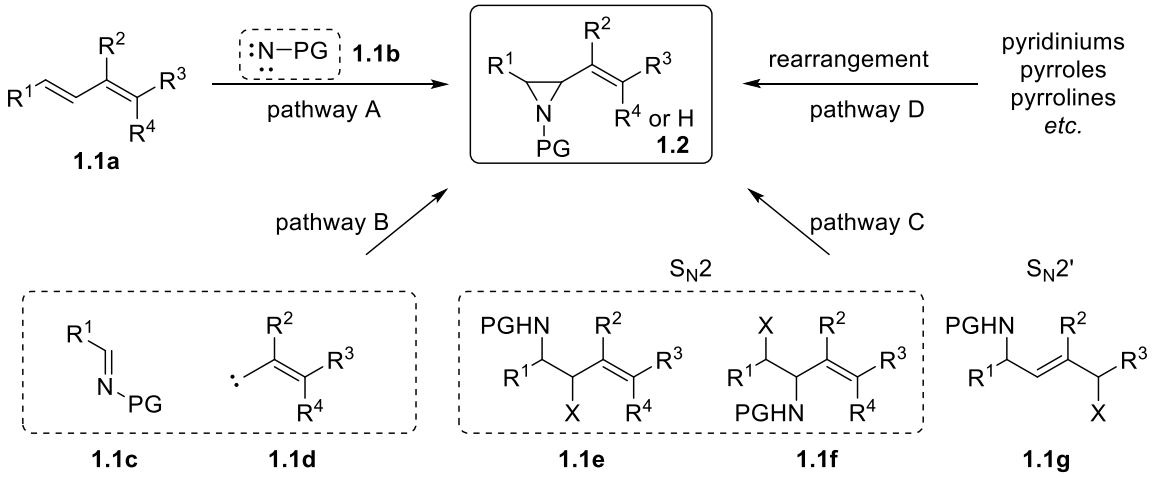
Chapter 1: Transition-Metal-Catalyzed Enantioselective Reactions of Vinyl aziridines

1.1 INTRODUCTION

Due to the strain energy of the three-membered ring, aziridines are one of the most versatile intermediates in organic synthesis towards a large number of biologically active molecules.[1] As useful building blocks, vinyl aziridines (Scheme 1.1) are increasingly being exploited comparing to the aziridines with other functional groups.[2] Due to the presence of the vinyl group substituents, the stabilities of any positive or negative charges and radicals generated during the transformations were greatly enhanced.

The transition-metal-catalyzed reaction of vinyl aziridines has proven to be a useful strategy for organic chemical synthesis. In many cases, the highly enantioselective version of this transformation can be achieved to generate ring-opening products. This review presents developments in transition-metal-catalyzed enantioselective reactions of vinyl aziridines, but the Lewis acids catalyzed ring-opening reactions will not be discussed.

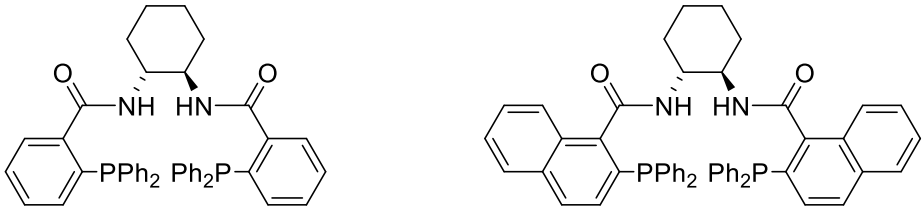


Scheme 1.1 General methods for synthesizing vinyl aziridines.

1.2 TRANSFORMATIONS FROM RACEMIC VINYL AZIRIDINES

1.2.1 Palladium Catalysis

The dynamic kinetic asymmetric transformations (DYKATs) of racemic starting material are efficient and atom economic synthetic methods in organic synthesis.[3] In the years before 2003, Trost and co-workers developed a highly efficient enantioselective process for the DYKATs of vinyl epoxides. By using Trost ligands (**1.3** and **1.4**, Figure 1.1), nucleophiles, such as alcohols, amines, phthalimides and acetoacetates, were utilized in these transformations.[4] Compared to vinyl epoxides, vinyl aziridines are usually considered less reactive in nucleophilic addition reactions.

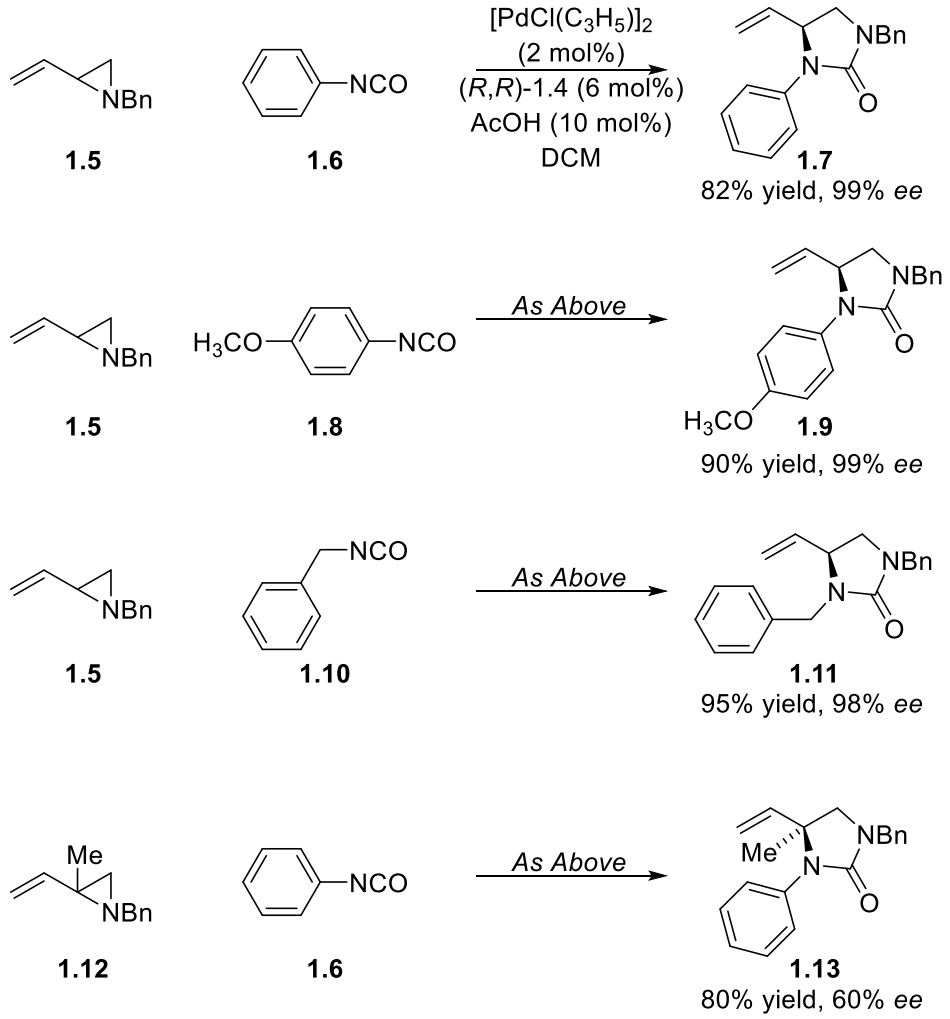


(*R, R*)-1.3 (*R, R*)-1.4

Figure 1.1 Trost ligands for DYKATs process.

In 2003, Trost and co-workers reported the Pd-catalyzed dynamic kinetic asymmetric cycloadditions of isocyanates to vinyl aziridines.[5a] Initial experiments were carried out under the condition of 4 mol% $Pd(OAc)_2$ and 10 mol% (*R*,*R*)-**1.3** while using *N*-benzyl vinyl aziridine **1.5** and phenyl isocyanate **1.6** as testing system. During a 24 h reaction time, the product **1.7** was obtained in 29% yield with 59% *ee*. After inclusive optimizations of the reaction conditions, including palladium precatalysts, ligands, additives, solvents, reaction time and temperature, the desired product was obtained with

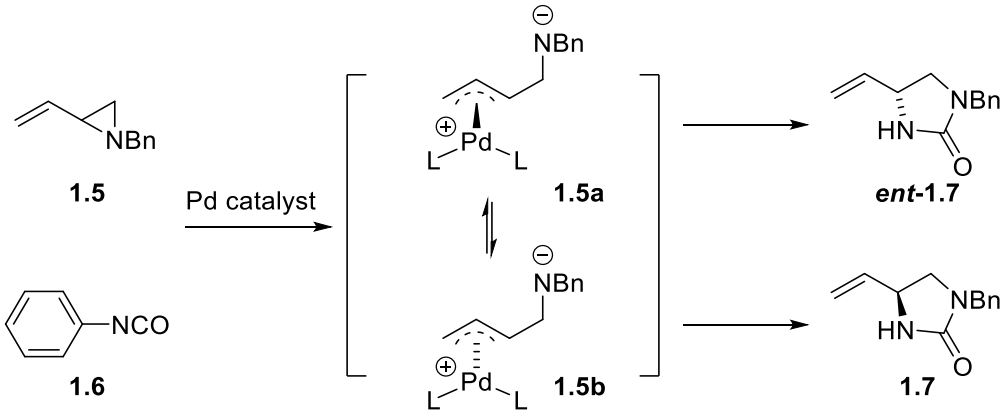
high enantiomeric excess. Under the optimized conditions, the scope of the vinyl aziridines and isocyanates was tested (Scheme 1.2).



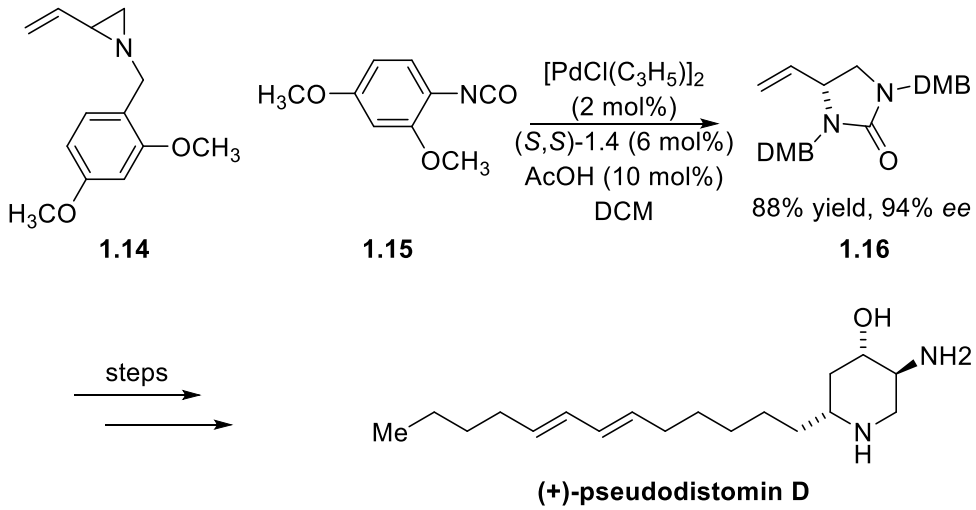
Scheme 1.2 Selected examples of asymmetric cycloadditions of vinyl aziridines and isocyanates.

One of the differences between the original reaction conditions and the optimized reaction condition is the AcOH additive. The reason is that in order to achieve high *ee* in this DYKATs process, the rate of equilibration between the diastereomeric π-allyl palladium intermediates (**1.5a** and **1.5b**) must be higher than the cyclization event (Scheme

1.3). Upon ring-opening of vinyl aziridine, the nitrogen was protonated by AcOH. As a consequence, addition to the isocyanate of the nitrogen slowed down. Thus, the η^3- η^1- η^3 interconversion of the π-allyl palladium intermediates occurred effectively which leads to the products with high enantioselectivity. Similarly, Alper and co-workers also found the addition of $CeCl_3$ may possibly increase the rate of interconversion of the π-allyl palladium intermediates.[5b]



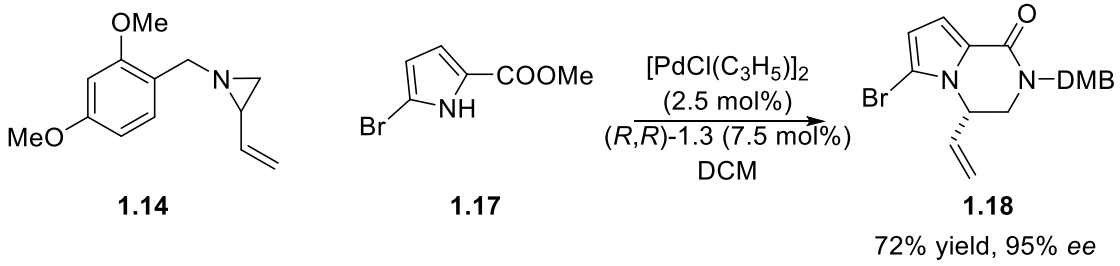
Scheme 1.3 Interconversion of the diastereomeric π-allyl palladium intermediates.



Scheme 1.4 Synthesis of (+)-pseudodistomin D.

Two years later in 2005, Trost and Fandrick applied the DYKATs, which is Pd-catalyzed dynamic kinetic asymmetric cycloadditions of isocyanates to vinyl aziridine, to the total synthesis of a pseudodistomin alkaloid natural product.[6] It turned out that Pseudodistomin D, which was isolated from ascidian *Pseudodistormina megalarva*, has potent cytotoxicity against human epidermoid carcinoma KB cells.[7] As shown in Scheme 1.4, the 1,2-chiral diamine **1.16**, which is the key intermediate, was constructed using Pd-catalyzed DYKATs process. This first total synthesis of pseudodistomin D demonstrated the importance of the Pd-catalyzed dynamic kinetic asymmetric cycloadditions of isocyanates to vinyl aziridines.

Bromopyrrole alkaloids are a family of marine natural products which shows various biological activities.[8] It turned out that pyrrolopiperazinone derivatives are the key substructures of a number of bromopyrrole alkaloids. In 2007, using the similar strategy, Trost and co-workers developed the Pd-catalyzed asymmetric alkylation-annulation reactions of methyl 5-bromopyrrole-2-carboxylate (**1.17**) and vinyl aziridine (**1.14**) to prepare pyrrolopiperazinone (**1.18**, Scheme 1.5).[9]



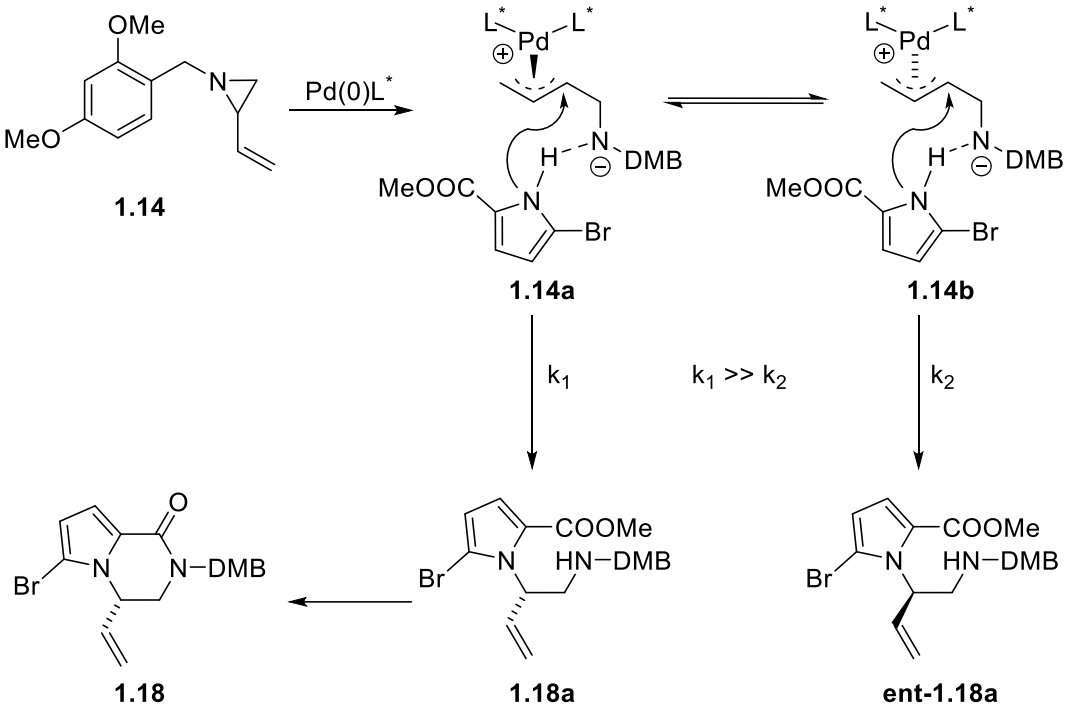
1.14 **1.17** **1.18**

72% yield, 95% *ee*

Scheme 1.5 Pd-catalyzed asymmetric alkylation-annulation of methyl 5-bromopyrrole-2-carboxylate and vinyl aziridine.

The mechanism of the asymmetric alkylation-annulation is shown in Scheme 1.6.[9] In the presence of Pd(0) complex, both enantiomers of vinyl aziridine were ionized while

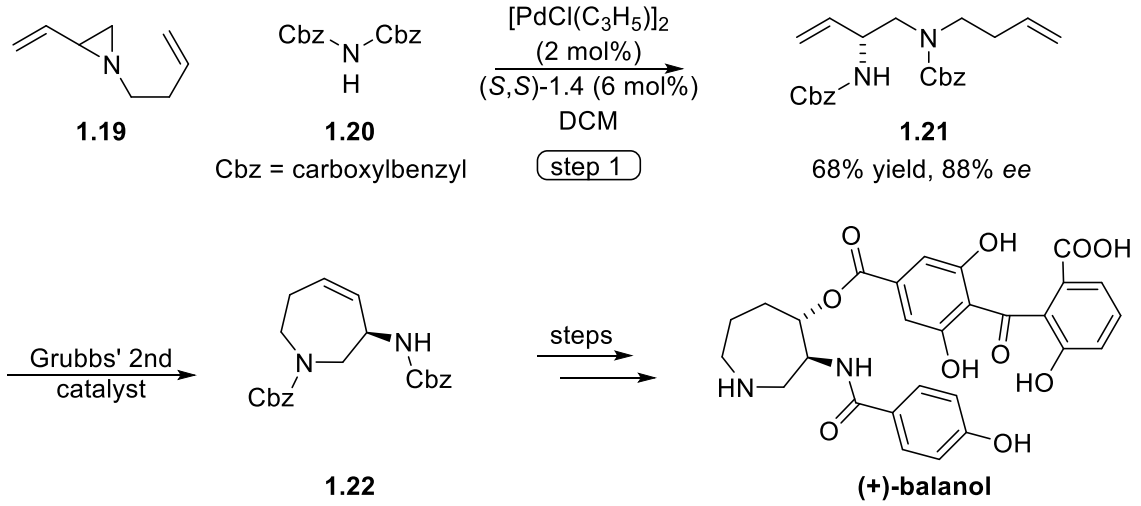
the hydrogen on the nitrogen of the pyrrole serves as a proton source to assist the ring-opening event. The asymmetric induction was achieved due to the interconversion between the two diastereomeric π-allyl palladium intermediates (**1.14a** and **1.14b**) was faster than the following nucleophilic addition. Thus, a Curtin-Hammett situation was generated wherein the enantiodiscriminating event was the amination reaction.



Scheme 1.6 Mechanism of the Pd-catalyzed asymmetric alkylation-annulation.

In the same year, instead of taking pyrrole as nitrogen source, Trost and co-workers reported the Pd-catalyzed asymmetric amination of vinyl aziridines by using benzoyl imido carboxylates as nitrogen source.[10] In these transformations, the desired products, orthogonally protected chiral vicinal diamines, were obtained with excellent yields and good to excellent enantioselectivities through amination and in situ acyl migration (step 1

in Scheme 1.7). The authors also demonstrated the utility of the asymmetric amination reaction by doing a formal synthesis of (+)-balanol. As shown in Scheme 1.7, the key intermediate **1.21**, chiral vicinal diamine, was prepared by the Pd-catalyzed asymmetric amination with good yield and enantioselectivity. By far, the Pd-catalyzed DYKATs of vinyl aziridines have proven to be powerful tools for the construction of stereocenters and have produced various methods for the synthesis of natural products.

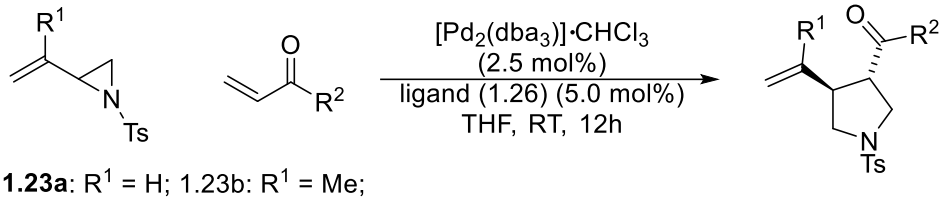


Scheme 1.7 Formal synthesis of (+)-balanol.

In 2015, Hou and Ding showed the highly diastereo- and enantioselective palladium-catalyzed [3+2] cycloaddition of vinyl aziridines and α,β-unsaturated ketones.[11] One of the strategies to prepare pyrrolidines, which is an important substructure of a number of natural products and biologically active molecules,[12] is transition-metal-catalyzed [3+2] cycloaddition of vinyl aziridines and alkenes with electron withdrawing groups.[13] Before 2015, there was no enantioselective version of the transformation aforementioned although a number of methods have been developed by chemists.[14] By using palladium catalyst modified by ferrocene-based ligand, Hou and Ding developed the

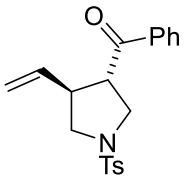
first enantioselective version of tandem Michael addition/intramolecular cyclization of vinyl aziridines with α,β-unsaturated ketones (Table 1.1). In general, the substituent group R^1 has been played an important role in the *cis*/*trans* selectivity.

Table 1.1 [3+2] cycloaddition of vinyl aziridine and α,β-unsaturated ketones.

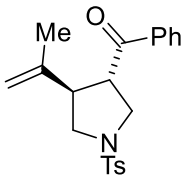


1.23a: R^1 = H; 1.23b: R^1 = Me;
1.24a: R^2 = Ph; 1.24b: R^2 = Me; 1.24c: R^2 = 2-furanyl

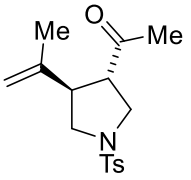
1.25



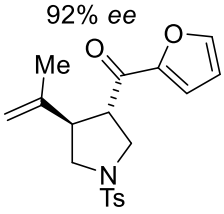
1.25aa: 94% yield,
2:1 *cis:trans*
94% *ee*



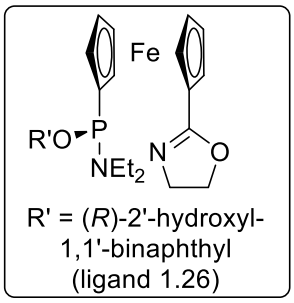
1.25ba: 78% yield,
13:1 *cis:trans*
92% *ee*



1.25bb: 85% yield,
23:1 *cis:trans*
95% *ee*



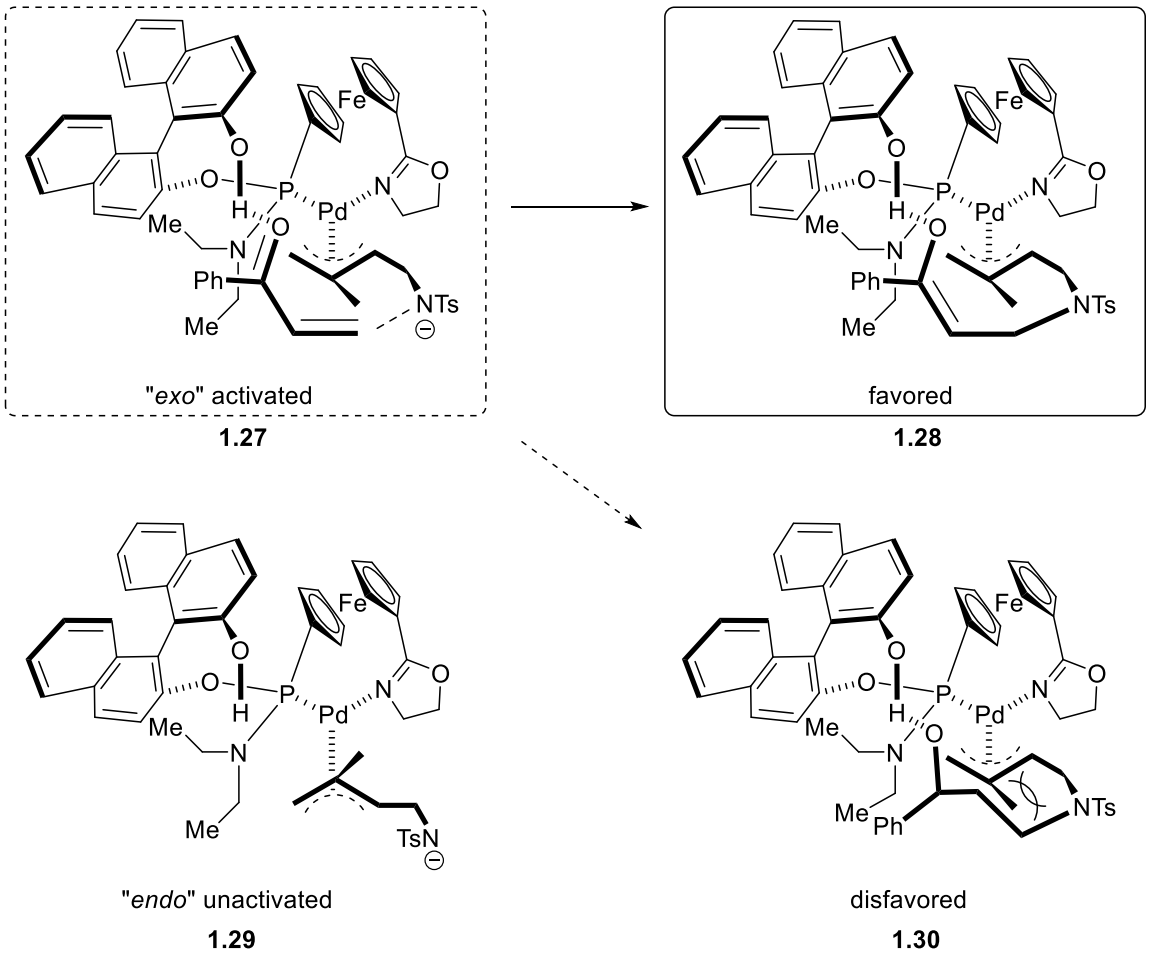
1.25bc: 74% yield,
12:1 *cis:trans*
63% *ee*



R' = (*R*)-2'-hydroxyl-1,1'-binaphthyl (ligand 1.26)

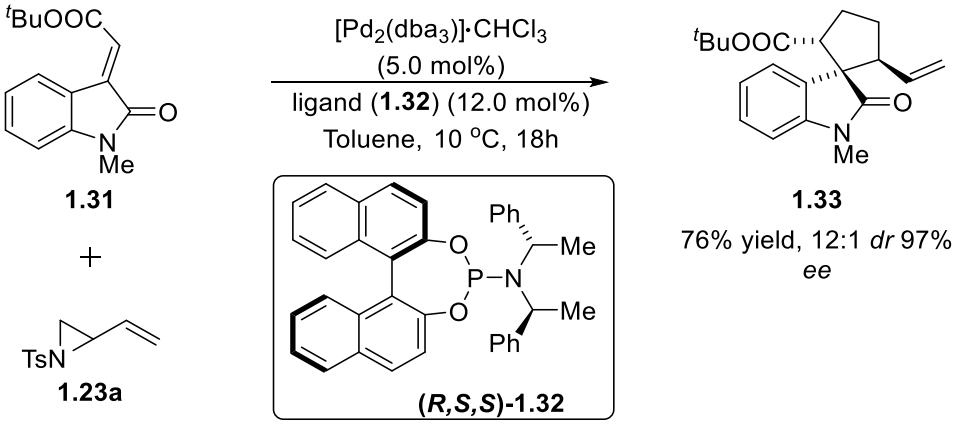
With the absolute configuration of products **1.25** in hand, the authors proposed a stereochemical model to explain the diastereo- and enantioselectivity of the asymmetric cycloaddition (Scheme 1.8). After the tosyl-protected nitrogen anion generation due to the π-allyl palladium formation, the nitrogen anion attacks the vinyl ketone to form an enolate intermediate. Following that, the enolate attacks the π-allyl palladium complex to form the desired cycloaddition product. Compared to the *endo* transition state **1.29**, the author

proposed the *exo* transition state **1.27** should be favored according to the X-ray diffraction analysis of the π-phenylallyl palladium complex with ligand **1.26**. At the same time, the methyl group at *C*2 position of the allyl substructure is of great importance to improve the diastereoselectivity. As shown in the complex **1.30**, the steric congestion between the enolate moiety and methyl group leads to a higher energy in complex **1.30**. In contrast, there is no severe steric congestion in the structure of complex **1.28**, which makes it favored.



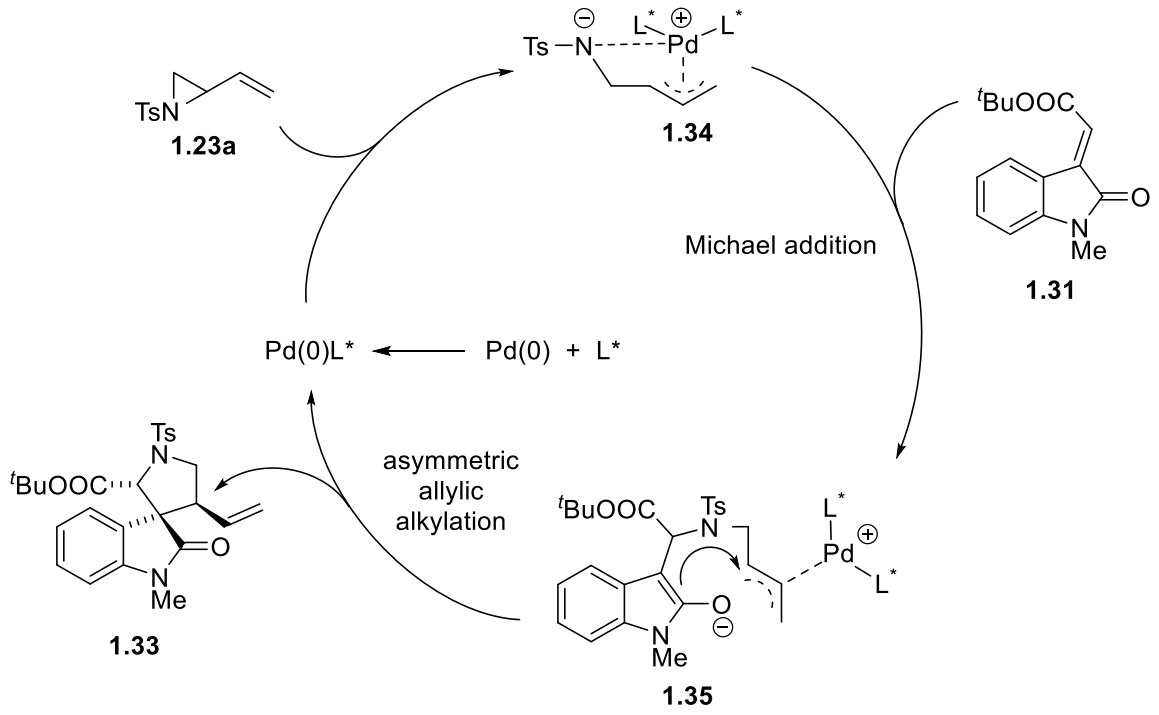
Scheme 1.8 Proposed stereochemical model for the diastereo- and enantioselectivity.

One year later, Lu and co-workers continued the studies of Pd-catalyzed [3+2] cycloaddition of vinyl aziridine with methyleneindolinones in 2016.[15] Spirooxindole derivatives exist in many natural products and biologically active compounds as substructure.[16] Using $Pd_2(dba)_3$ as precatalyst, Lu and co-workers optimized the different chiral phosphoramidate ligands for the transformations to form spirooxindole products. Eventually, as shown in Scheme 1.9, ligand (*R,S,S*)-**1.32** was the best ligand for the [3+2] cycloaddition reactions.



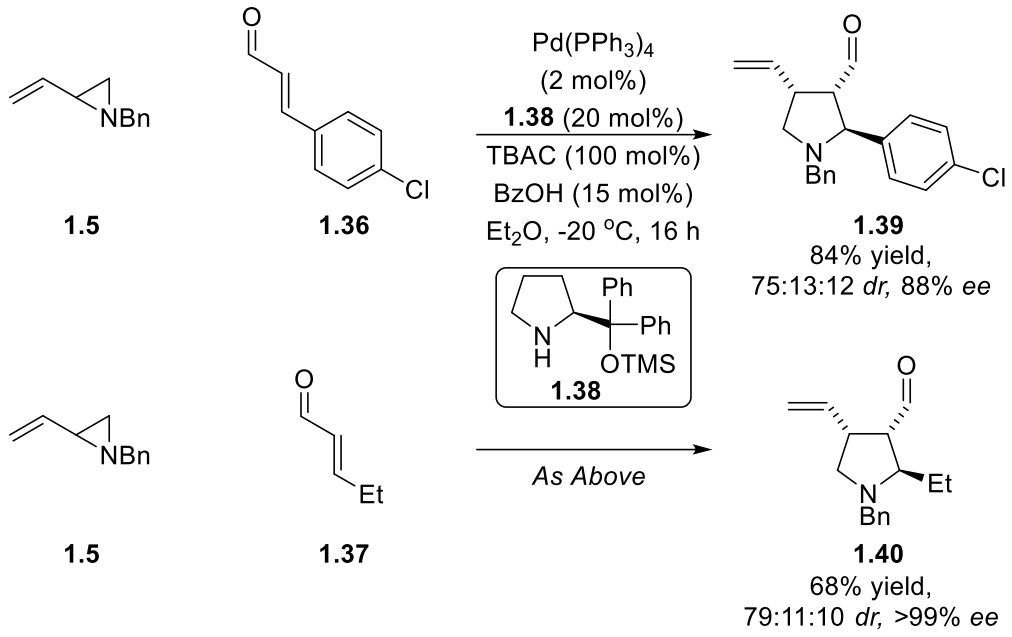
Scheme 1.9 [3+2] cycloaddition of vinyl aziridine with methyleneindolinones.

To gain insight into the catalytic mechanism, the authors proposed a catalytic cycle for the [3+2] cycloaddition reaction (Scheme 1.10). The chiral π-allyl palladium species **1.34** was generated from vinyl aziridine **1.23a** upon ring-opening by Pd(0) catalyst. Michael addition to methyleneindolinone **1.31** occurred to generate the zwitterionic intermediate **1.35**. Then, intramolecular asymmetric allylic alkylation reaction happened to form the spirooxindole product **1.33**, at the same time regenerated the Pd(0) complex.



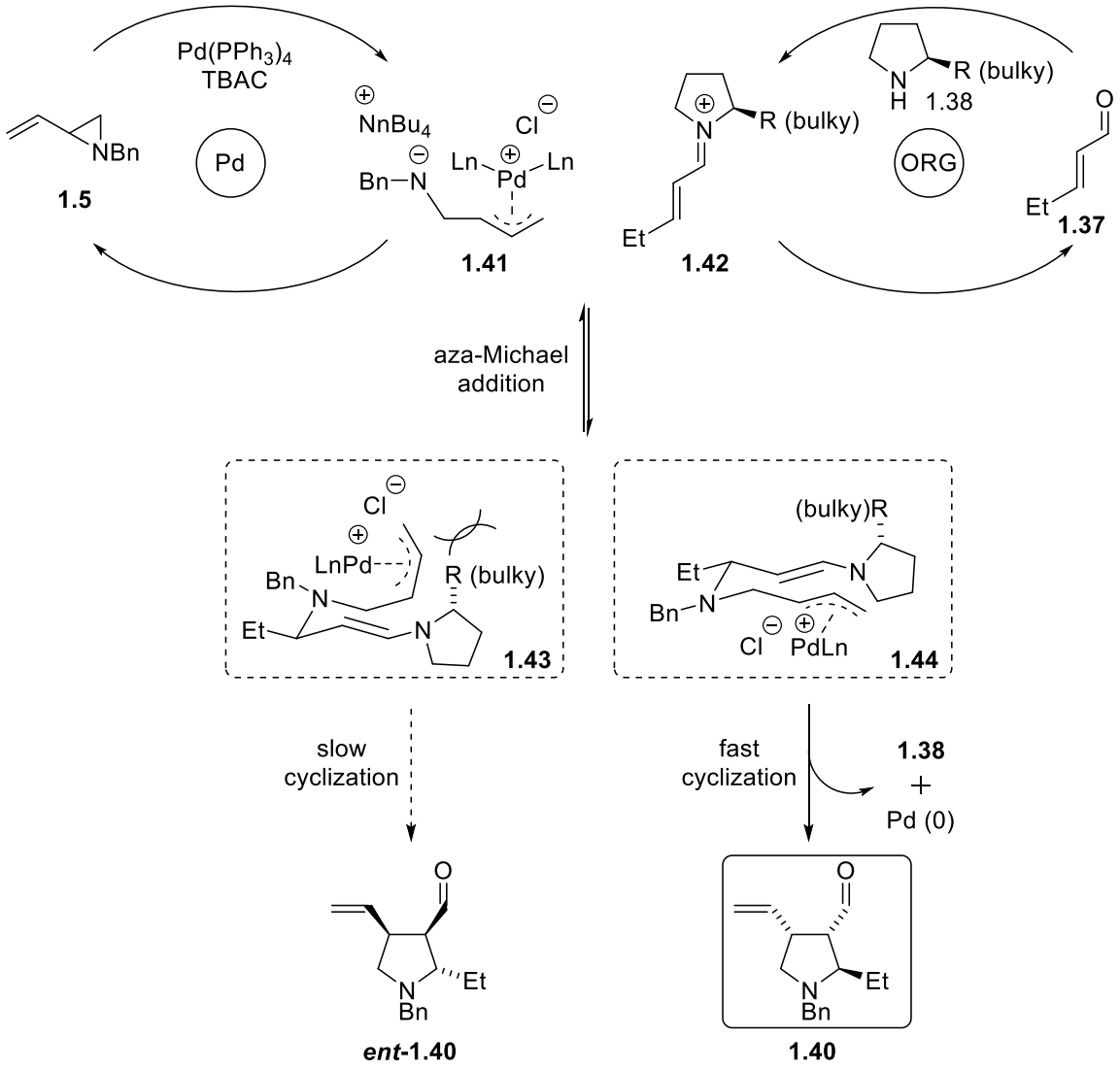
Scheme 1.10 Proposed catalytic mechanism for [3+2] cycloaddition reactions.

Synergistic catalysis, which was developed by combining aminocatalysis with transition-metal catalysis, is an attractive topic in organic chemical synthesis.[17] Inspired by the previous works of synergistic catalysis, Jørgensen and co-workers reported the synergistic catalysis for the asymmetric [3+2] cycloaddition of vinyl aziridines with α,β-unsaturated aldehydes in 2017.[18] Under the condition of co-catalysts diphenylprolinolsilyl ether **1.38** and Tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$), in the presence of tetrabutylammonium chloride (TBAC) and benzoic acid, the desired [3+2] cycloaddition products can be obtained in good yields, good diastereoselectivity and excellent enantioselectivity (Scheme 1.11). As shown in Scheme 1.11, both aromatic substituted and aliphatic substituted α,β-unsaturated aldehydes worked well under the optimized reaction conditions.



Scheme 1.11 Synergistic catalysis for the asymmetric [3+2] cycloaddition.

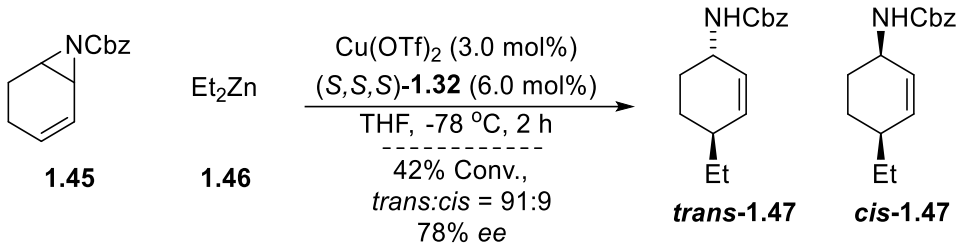
As shown in Scheme 1.12, Jørgensen and co-workers proposed a catalytic mechanism for the aforementioned asymmetric [3+2] cycloaddition reactions. After the event of ring-opening of vinyl aziridine **1.5** by Pd(0) catalyst through oxidative addition, the zwitterionic π-allyl palladium (II) complex **1.41** was formed. On the other hand, the iminium ion intermediate **1.42** was formed from the organocatalyst **1.38** and α,β-unsaturated aldehyde **1.37** through condensation. Then, a reversible aza-Michael addition process occurred between intermediates **1.41** and **1.42** to generate a pair of diastereomeric intermediates **1.43** and **1.44**. Due to the steric congestion of the π-allyl palladium moiety and the bulky group on the *C*2 position of the organocatalyst, cyclization of intermediate **1.43** was much slower than intermediate **1.44**. As a consequence, the *Si* face of the chiral enamine of intermediate **1.44** underwent cyclization. To complete the synergistic catalytic cycle, upon decomplexation of the Pd(0) and hydrolysis of iminium ion, both catalysts were regenerated.



Scheme 1.12 Proposed mechanism of the synergistic catalysis for the asymmetric [3+2] cycloaddition.

1.2.2 Copper Catalysis

In 2003, Pineschi and co-workers reported the regio- and enantioselective copper catalyzed addition of dialkylzinc reagents to cyclic vinyl aziridines.[19] When the $Cu(OTf)_2$ was employed as catalyst, the addition of Et_2Zn to vinyl aziridine **1.45** occurred smoothly to produce allylic amine product **1.47** with 78% *ee* for the *trans*-isomer (Scheme 1.13).



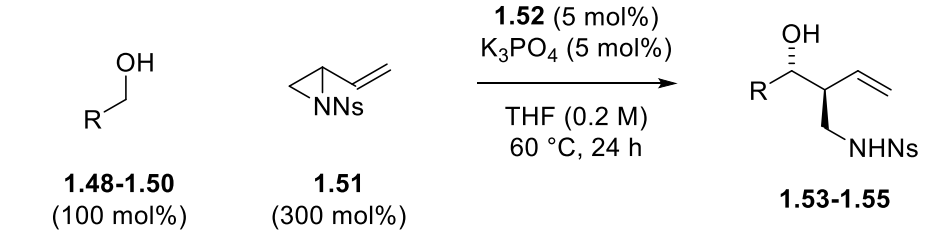
Scheme 1.13 Copper catalyzed addition of organozinc reagent to vinyl aziridine.

1.2.3 Iridium Catalysis

Redox-triggered carbonyl addition via transfer hydrogenation enables direct primary alcohol C−H functionalization in the absence of premetalated reagents or discrete alcohol to aldehyde redox reactions.[20] Functionalized piperidines appear frequently as substructures in a number of natural alkaloids and pharmaceutical ingredients.[21] In fact, the piperidine ring is the third most frequently used ring system in small molecule drugs listed in the FDA orange book.[22] Therefore, developing methods to diastereoselectively synthesize piperidine has drawn a great deal of attention.[23]

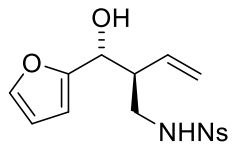
Because of the competing electrophilic of *O*-allylation of the resulting π-allyliridium complexes,[24] along with the propensity of vinyl aziridines to participate in metal catalyzed ring expansion, the feasibility of engaging vinyl aziridines in metal catalyzed C-C couplings with primary alcohols was rendered uncertain. Despite these potential liabilities, Krische and co-workers developed the diastereo- and enantioselective iridium catalyzed coupling of vinyl aziridines with alcohols in 2015.[25] As shown in Table 1.2, diverse primary alcohols **1.48**-**1.50** (100 mol%) were exposed to vinyl aziridine **1.51** (300 mol%) in the presence of complex **1.52** (5 mol%) and substoichiometric potassium phosphate (5 mol%) in THF (0.5 M) at 60 ºC, in which the desired products **1.53**-**1.55** were obtained with good yields, good *anti*-diastereoselectivity and excellent enantioselectivity.

Table 1.2 Diastereo- and enantioselective iridium catalyzed (α-aminomethyl)allylation of alcohols with vinyl aziridine.

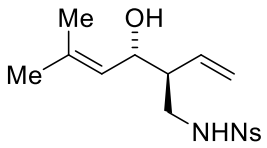


1.48-1.50 (100 mol%) | **1.51** (300 mol%) | **1.53-1.55**

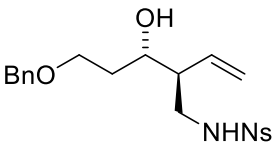
1.48, R = 2-furyl, 1.49, R = $CH{=}CMe_2$, 1.50, R = $(CH_2)_2OBn$



1.53, 73% Yield
10:1 *dr*, 97% *ee*

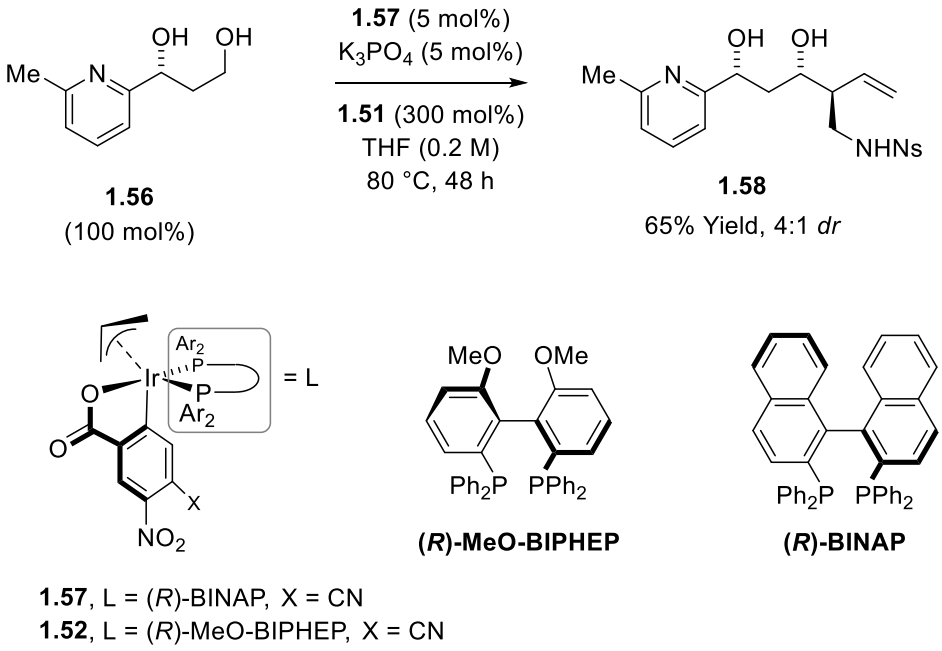


1.54, 70% Yield
8:1 *dr*, 95% *ee*



1.55, 87% Yield
8:1 *dr*, 98% *ee*

Having demonstrated the feasibility and scope of the coupling of primary alcohols, the catalyst-directed diastereo- and site-selective C-C coupling of unprotected diols with vinyl aziridine **1.51** was investigated. As shown in Scheme 1.14, the product of (α-aminomethyl)allylation **1.58** was formed in good yield and with good level of catalyst-directed diastereoselectivity. Conditions used in the coupling of primary alcohols were not directly transferable. Longer reaction times were required. In addition, the optimal pairing of diols and catalyst was case dependent. For example, in the coupling of diol **1.56** with vinyl aziridines **1.51**, the iridium catalyst **1.57**, which is modified by (*R*)-Cl,MeO-BIPHEP, gave slightly better results than catalyst **1.52**, which is modified by (*R*)-MeO-BIPHEP. Similarly, the iridium catalysts derived from the enantiomeric ligands have also been used in the aforementioned conversion of unprotected diols. In each case, the products of (α-aminomethyl)allylation were formed in good yield and with good level of catalyst-directed diastereoselectivity.



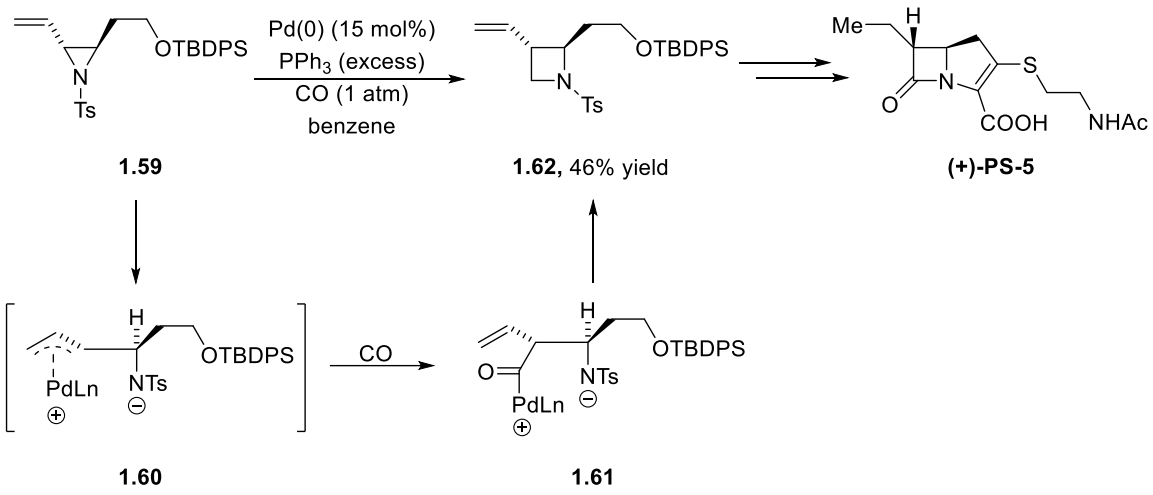
Scheme 1.14 Diastereoselective iridium catalyzed (α-aminomethyl)allylation of diol **1.56** with vinyl aziridine **1.51**.

1.3 Chirality Transfer Strategy: Transformations from Chiral Vinyl Aziridines

1.3.1 Palladium Catalysis

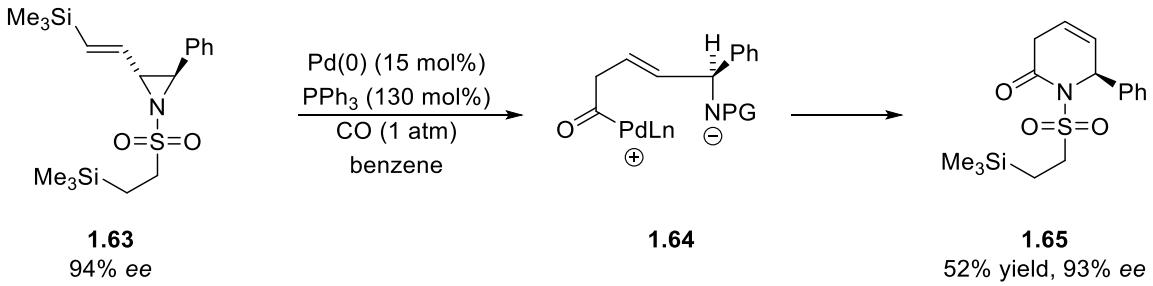
One of the most useful methods to prepare β-lactams is ring expansion of vinyl aziridines with carbon monoxide. In 1993, Tanner and Somfai[26] reported the palladium catalyzed transformation of a chiral vinyl aziridine to a β-lactam. Using this strategy, Tanner and Somfai succeeded in synthesizing (+)-PS-5 (Scheme 1.15). The optically pure vinyl aziridine **1.59** was utilized in the carbonylation reaction which was catalyzed by the $Pd_2(dba)_3$ and in the presence of excess amount of triphenylphosphine in benzene. The desired *trans*-3-vinylazetidinone **1.62** was obtained in 46% yield. Stabilized by the intermolecular coordination of the nitrogen anion, the π-allyl palladium complex **1.60** was

formed through inversion. Upon the insertion of carbon monoxide with retention, ring-closure and regeneration of Pd(0) species occurred.



Scheme 1.15 Pd-catalyzed carbonylative ring expansion to β-lactam.

Interestingly, in 2001, Aggarwal and co-workers reported a similar transformation but with different regioselectivity.[27] Under the reaction conditions, in the presence of Pd(0) catalyst and triphenylphosphine, the γ-lactam **1.65** was formed in moderate yield with 93% enantiomeric excess when using optically pure vinyl aziridine **1.63** as starting material (Scheme 1.16). The origins of the selectivity for the γ-lactam is under further investigation.

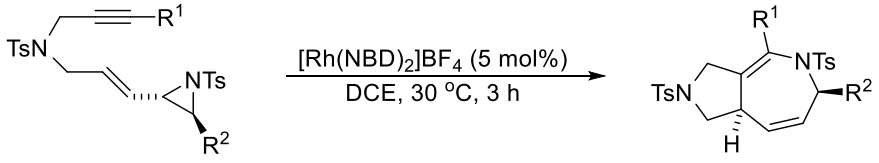


Scheme 1.16 Pd-catalyzed carbonylative ring expansion to γ-lactam.

1.3.2 Rhodium Catalysis

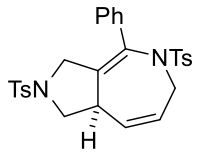
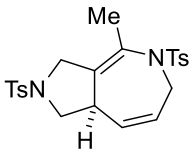
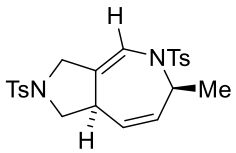
Although a number of methodologies have been developed for the formation of the seven-membered azaheterocycle structures,[28] the development of new cycloaddition transformations to achieve substituted, ring-fused azepines from acyclic starting material remains highly desirable. In 2015, Zhang and co-workers developed the rhodium catalyzed intramolecular formal hetero-[5+2] cycloaddition of vinyl aziridines and alkynes.[29] Based on the chiral center preinstalled in vinyl aziridines, Zhang and co-workers could synthesize fused azepine derivatives in excellent enantioselectivity (Table 1.3). In the presence of the $[Rh(NBD)_2]BF_4$ catalyst, the intramolecular formal hetero-[5+2] cycloaddition process occurred smoothly at 30 °C in 1,2-dichloroethane. It turns out that the alkyne substitution could be an aryl, heteroaryl, alkyl or cyclohexenyl group. Remarkably, terminal alkynes have also been used in this transformation and excellent enantioselectivity was obtained. In addition, the substitutions on the vinyl aziridine ring were allowed to change from methyl, *n*-propyl to *i*-propyl group in which the reaction conditions were modified from the standard optimal conditions.

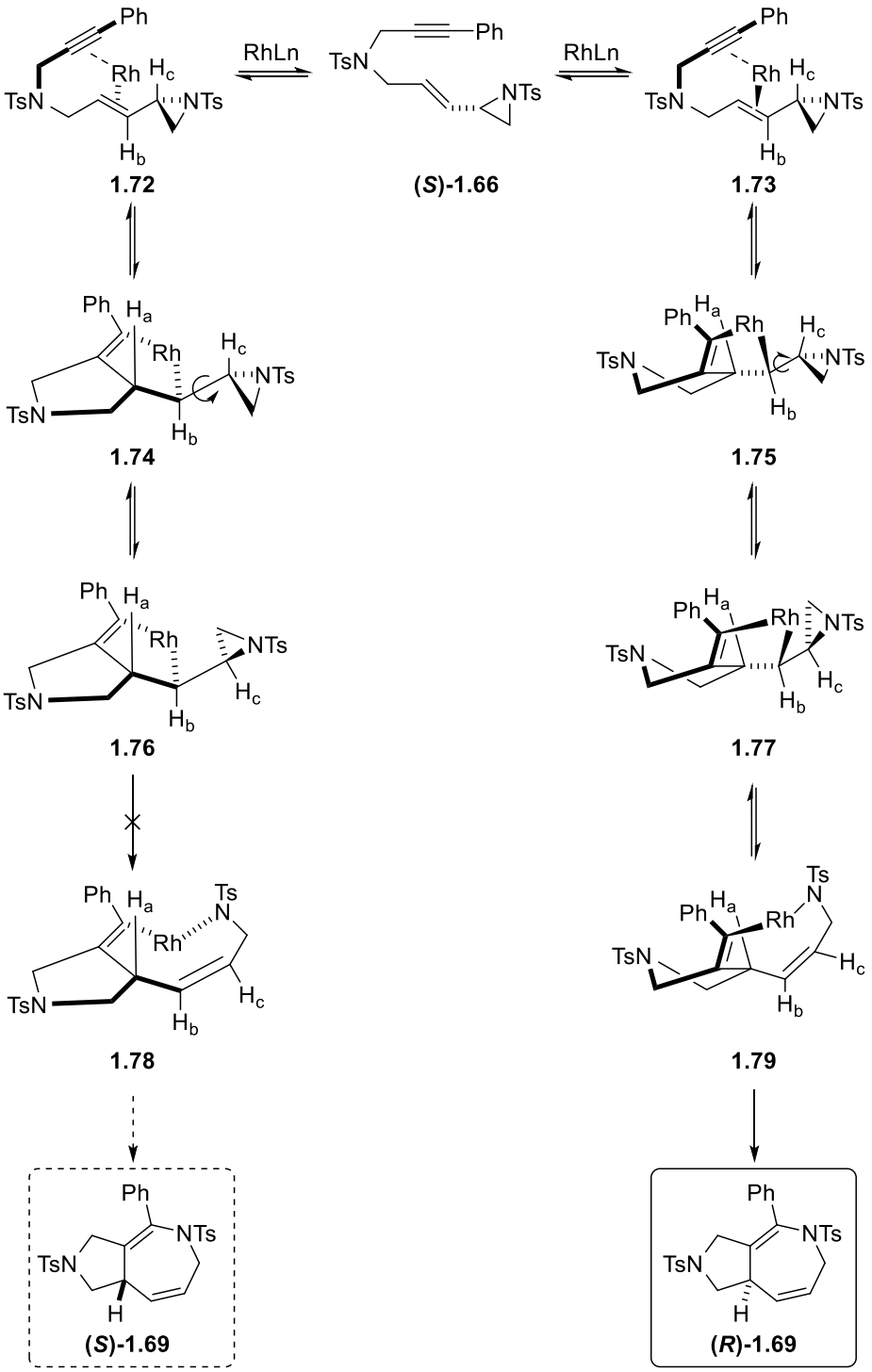
Table 1.3 Rh-catalyzed intramolecular reaction of vinyl aziridines with alkynes.



1.66-1.68 → **1.69-1.71**

1.66 (90% *ee*): R^1 = Ph, R^2 = H; **1.67** (84% *ee*): R^1 = Me, R^2 = H;
1.68 (>99% *ee*): R^1 = H, R^2 = Me

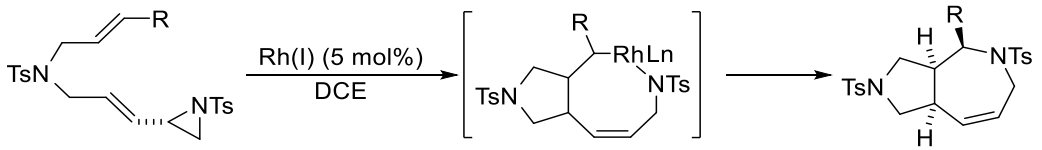
1.69	**1.70**	**1.71**
		
90% yield, 90% *ee*	95% yield, 85% *ee*	90% yield, >99% *ee*



Scheme 1.17 Stereochemical model for Rh-catalyzed intramolecular cycloaddition of vinyl aziridines with alkynes.

The proposed stereochemical model was proposed by Zhang and co-workers (Scheme 1.17), in which both faces of the C-C double bond in (*S*)-**1.66** could coordinate to the rhodium complex (**1.72** and **1.73**). In order to form a *Z*-olefin in **1.78** and **1.79**, protons H_b and H_c have to have a *syn* alignment relationship which was achieved through bond rotation to give **1.76** and **1.77**. However, only in **1.77** the C-N bond in the aziridine could suitably overlap with the C-Rh bond as required for the concerted ring expansion reaction. Thus, upon reductive elimination, the optically pure product (*R*)-**1.69** was obtained.

Inspired by the Rh-catalyzed cycloaddition reaction aforementioned, the Zhang group reported a similar intramolecular cycloaddition reaction of vinyl aziridines with alkenes.[30] As shown in Scheme 1.18, using chiral vinyl aziridines as starting material, in the presence of Rh catalyst, the desired cycloaddition products were formed in moderate to good yield with excellent enantioselectivity (up to 99% *ee*). Notably, using the chirality transfer strategy, three contiguous chiral stereocenters were formed in one step.

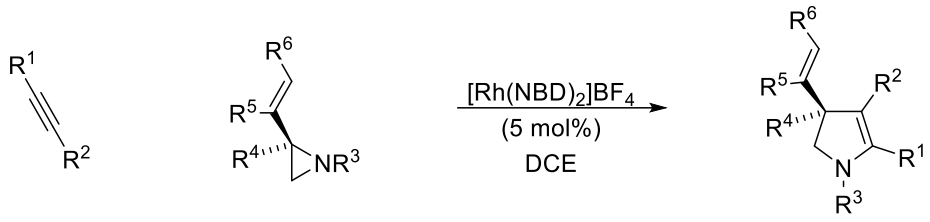


1.80 **1.81** **1.82**

Scheme 1.18 Rh-catalyzed intramolecular reaction of vinyl aziridines with alkenes.

After that, Zhang and co-workers started to explore the intermolecular version of the rhodium catalyzed cycloaddition reactions of vinyl aziridines with alkynes.[31] As shown in Scheme 1.19, in the presence of rhodium catalyst, the chiral vinyl aziridines (*R*)-**1.84** reacted with alkynes **1.83** to provide cycloaddition products **1.85** with excellent enantioselectivity (up to 99% *ee*). Additionally, the substrate scope is broad, for instance,

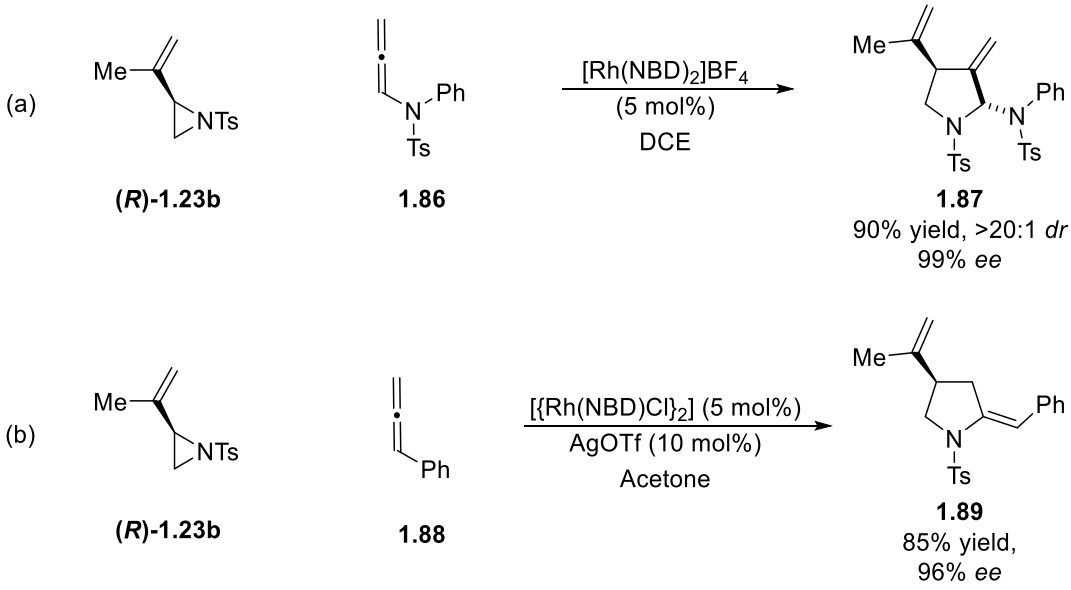
R^1 could be alkyl, aryl or silyl groups, while R^5 could be alkyl, aryl or oxygen atom with silyl groups.



1.83 **(*R*)-1.84** **1.85**
up to 99% *ee*

Scheme 1.19 Rh-catalyzed intermolecular reaction of vinyl aziridines with alkynes.

Later in the same year 2016, Zhang and co-workers applied substituted allenes in the rhodium catalyzed [3+2] cycloaddition reactions with chiral vinyl aziridines to synthesize chiral pyrrolidines (Scheme 1.20).[32] Remarkably, different regioselectivities were achieved in this rhodium catalyzed [3+2] cycloaddition.

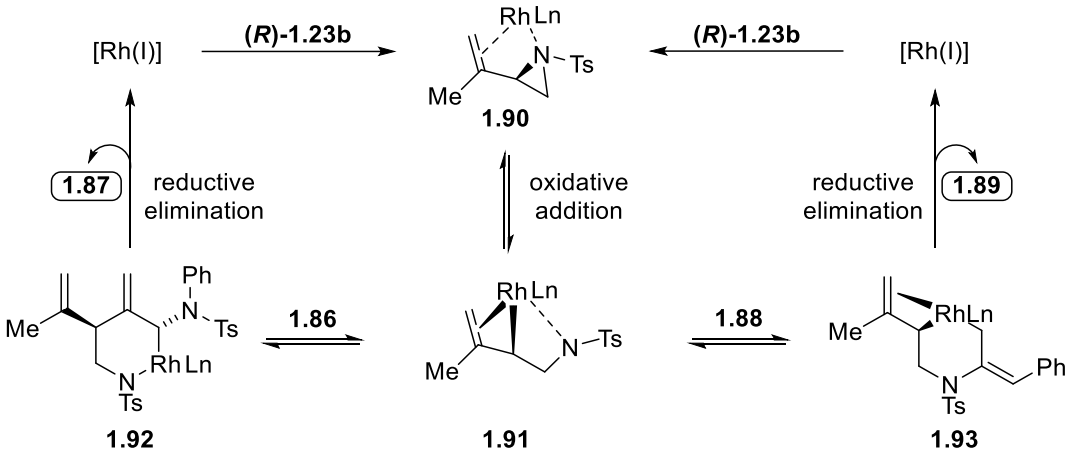


(*R*)-1.23b **1.86** **1.87**
90% yield, >20:1 *dr*
99% *ee*

(*R*)-1.23b **1.88** **1.89**
85% yield,
96% *ee*

Scheme 1.20 Rh-catalyzed intermolecular reaction of vinyl aziridines with allenes.

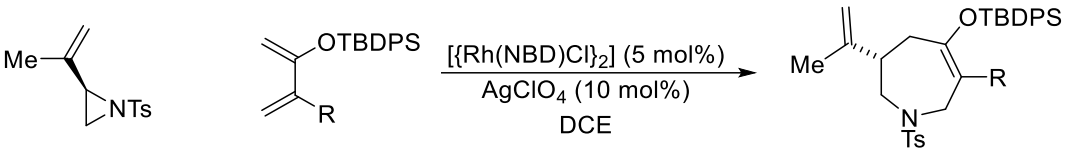
The mechanism was shown in Scheme 1.21, both alkene and amin coordinate to the rhodium catalyst to give rhodium complex **1.90**. Then oxidative addition occurred to provide complex **1.91** with retention of configuration. Subsequently, species **1.91** could be captured by the proximal C=C bond of **1.86** regioselectively which gave complex **1.92**. Upon reductive elimination, the rhodium(I) catalyst was regenerated while release the desired product **1.87**. Alternatively, the distal C=C bond of allene **1.88** was captured by complex **1.91**, which was followed by reductive elimination to provide product **1.89**.



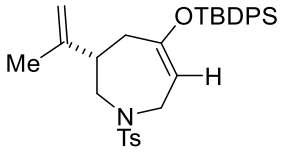
Scheme 1.21 Proposed mechanism for Rh-catalyzed intermolecular reaction of vinyl aziridines with allenes.

Continuing the chirality transfer strategy, Zhang group developed intermolecular aza-[4+3] cycloaddition of chiral vinyl aziridines with silyl dienol ethers by using rhodium catalyst (Table 1.4).[33] Using optically pure vinyl aziridines as starting material, in the presence of rhodium(I) catalyst and silver salt, the desired azepine derivative products were formed in good yields with excellent enantioselectivity. Different from the previous reports, net inversion of the absolute configuration was observed in this process.

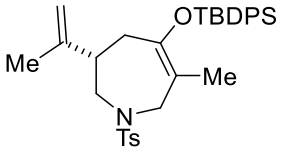
Table 1.4 Rh-catalyzed intermolecular reaction of vinyl aziridines with silyl dienol ethers.



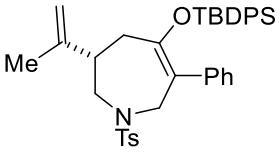
(*R*)-1.23b **1.94-1.96** **1.97-1.99**



1.97
55% yield, 96% *ee*

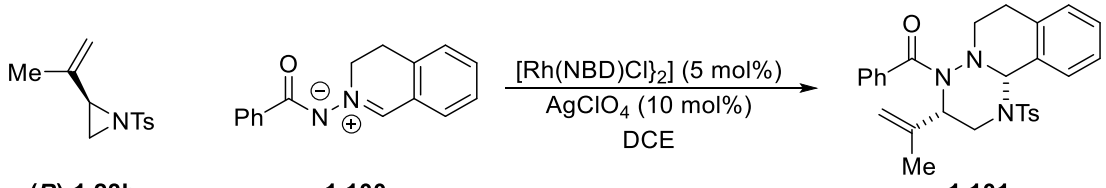


1.98
81% yield, 98% *ee*



1.99
90% yield, 98% *ee*

More recently, Zhang and co-workers developed rhodium catalyzed intermolecular [3+3] cycloaddition of chiral vinyl aziridines with C,N-cyclic azomethine imines (Scheme 1.22).[34] Taking advantages of the chirality transfer strategy, Zhang group developed the first rhodium catalyzed [(aza-3C)+(aza-3C)] cycloaddition reaction, which provided the chiral fused tricyclic 1,2,4-hexahydrotriazines in good yields with excellent diastereoselectivity and enantioselectivity.



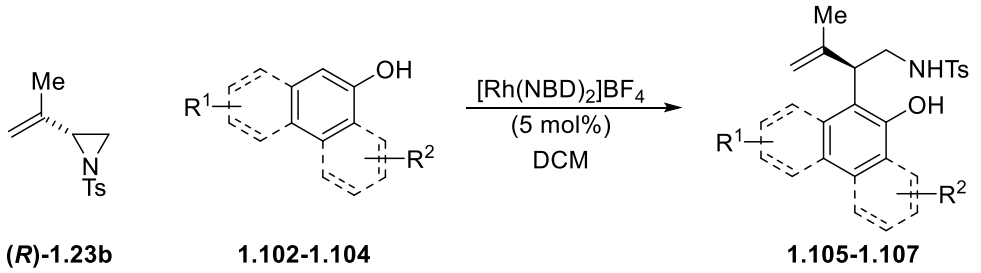
(*R*)-1.23b **1.100**

1.101
80% yield, >20:1 *dr*
95% *ee*

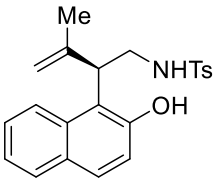
Scheme 1.22 Rh-catalyzed intermolecular [3+3] cycloaddition of vinyl aziridines with *C,N*-cyclic azomethine imines.

Another example of chirality transfer strategy by using chiral vinyl aziridines is rhodium catalyzed chemoselective and regioselective allylic alkylation of hydroxyarenes with chiral vinyl aziridines, which from Zhang group in 2017.[35] As shown in Table 1.5, either naphthols or phenols could be applied in this transformation to serve as *C*-nucleophiles rather than *O*-nucleophiles. By using chirality transfer strategy, this reaction provide a useful, efficient way to synthesize 2-arylethylamine derivatives in an enantioselective manner.

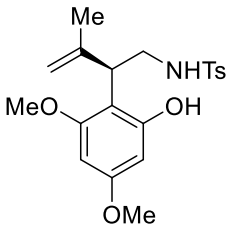
Table 1.5 Rh-catalyzed intermolecular reaction of vinyl aziridines with naphthols and phenols.



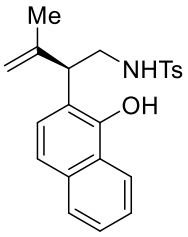
(*R*)-1.23b **1.102-1.104** **1.105-1.107**



1.105
92% yield,
94% *ee*



1.106
77% yield,
97% *ee*

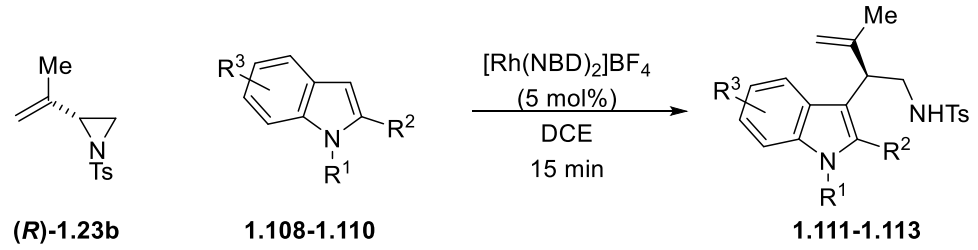


1.107
30% yield,
83% *ee*

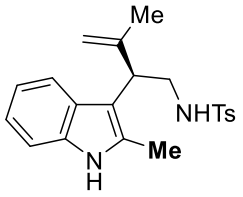
More recently this year, Zhang group disclosed work of enantioselective rhodium catalyzed allylic substitutions of vinyl aziridines and indoles.[36] As shown in Table 1.6, different substituted indoles were applied in this enantioselective transformation. The desired products β-vinyltryptamines, were obtained in good to excellent yields with

excellent enentioselectivity when the optically pure vinyl aziridines were utilized as allyl donors.

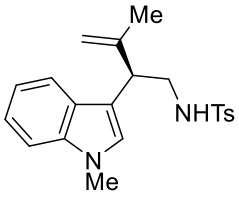
Table 1.6 Rh-catalyzed allylic substitutions of vinyl aziridines and indoles.



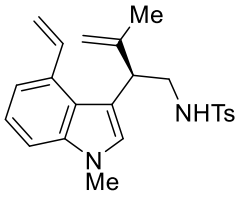
(*R*)-1.23b | 1.108-1.110 | 1.111-1.113



1.111
99% yield,
98% *ee*



1.112
85% yield,
98% *ee*



1.113
80% yield,
97% *ee*

1.4 CONCLUSION

This review summarizes transition-metal-catalyzed enantioselective reactions of vinyl aziridines. Vinyl aziridines are versatile building blocks for synthesis of many different compounds which contain nitrogen atoms. The ring strain of aziridines at the reactive allylic position greatly enhanced the reactivity towards a number of transition-metal-catalyzed enantioselective transformations, including cycloaddition, carbonyl addition, as well as alkylation reactions to provide a range of useful molecules which contain nitrogen. The transition-metal-catalyzed enantioselective transformations of vinyl aziridines will be increasingly useful and important since the growing of interest in nitrogen-containing compounds from organic and medicinal chemistry. It's reasonable to

expect that new efficient enantioselective methodologies involving vinyl aziridines will be disclosed in the near future, which could provide other approaches to a variety of optically pure nitrogen-containing molecules.

Chapter 2: Catalyst-Directed Diastereo- and Site-Selectivity in Successive Nucleophilic and Electrophilic Allylations of Chiral 1,3-Diols: Protecting-Group-Free Synthesis of Substituted Pyrans*

2.1 Introduction

The site-selective transformation of polyfunctional molecules greatly enhances the step-economy since no protecting groups is needed.[1] A number of methods[2] were developed for the site-selective modification of carbohydrates and other natural polyols which provides direct access to compounds that otherwise would require numerous steps to prepare. The cyclometalated π-allyliridium catalysts used in the redox-triggered alcohol C-H functionalization demonstrate a distinct kinetic preference for primary alcohol dehydrogenation,[3] facilitating site-selective C-H functionalization of unprotected diols and triols with high levels of catalyst-directed diastereoselectivity.[4]

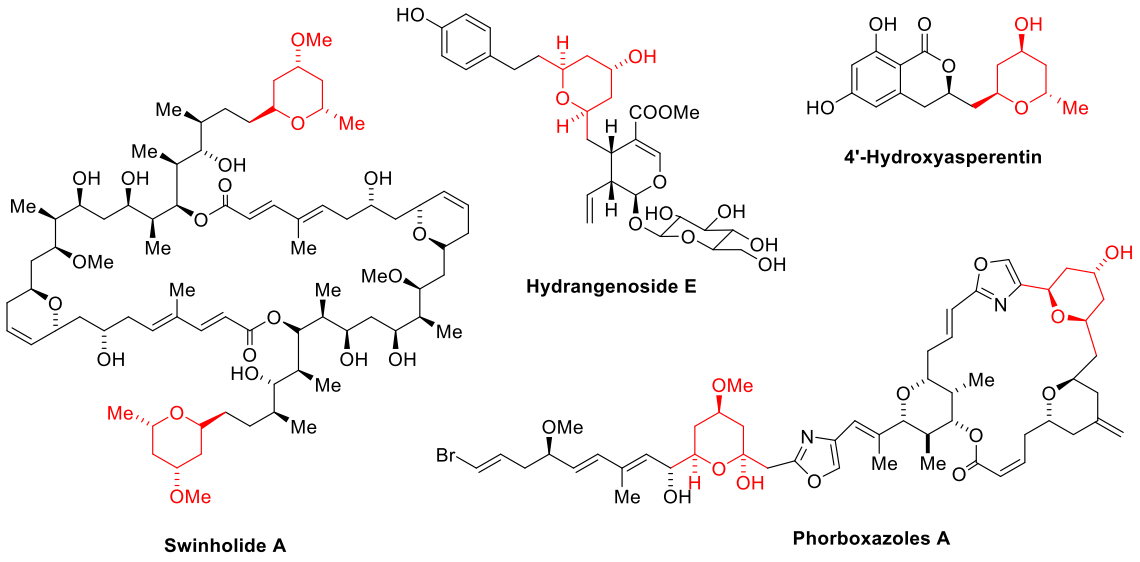
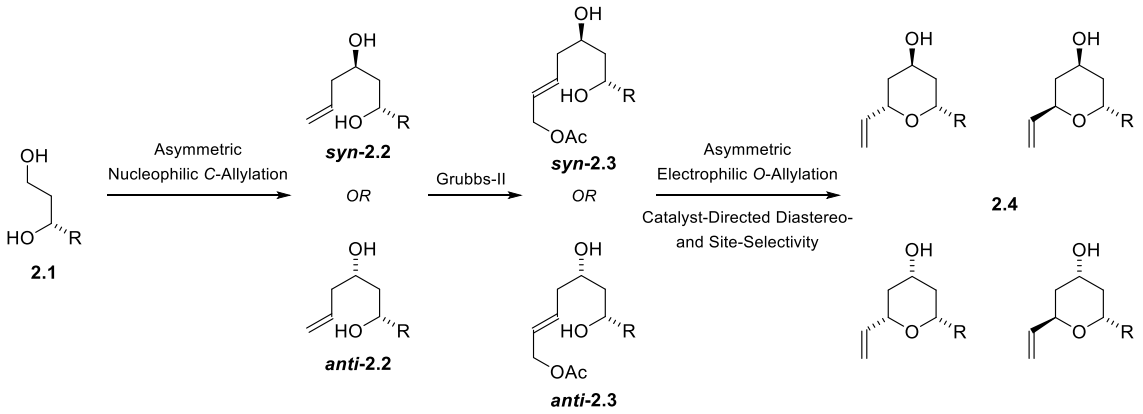


Figure 2.1 Representative natural products containing 4-hydroxy-2,6-disubstituted tetrahydropyran motif.[8]

* This chapter is based on the published work:
Shin, I.; Wang, G.; Krische, M. J. *Chem. Eur. J.* **2014**, *20*, 13382.

The 4-hydroxy-2,6-*cis*- or *trans*-disubstituted tetrahydropyrans are common moities incorporated in polyketide natural products (Figure. 2.1).[5] Complex poly-substituted pyrans are often formed via Prins cyclization, cycloetherification of olefinic alcohols triggered by electrophilic reagents (e.g. haloetherification), and oxa-Michael cyclization.[5] As documented in the literature,[6] the monoallylic alcohol cyclization can be catalyzed by carbophilic metals to form the pyran ring.

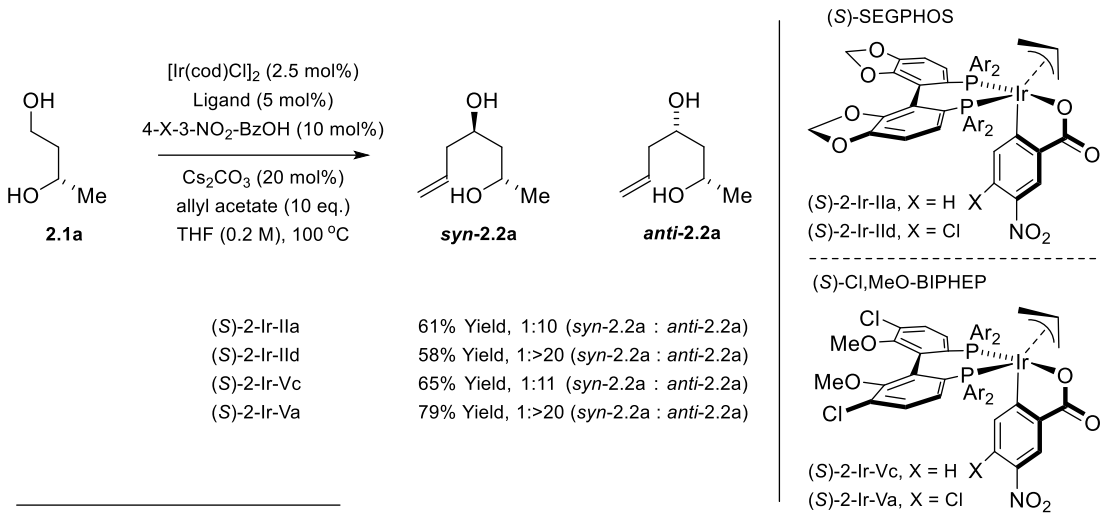


Scheme 2.1 Iridium catalyzed diastereo- and site-selectivity in successive nucleophilic and electrophilic allylations of chiral 1,3-diols.

2.2 Reaction Development and Scope

We disclose a strategy for pyran formation involving iridium-catalyzed diastereo- and site-selective *C*-allylation of chiral 1,3-diols, which followed by Grubbs metathesis and metal-catalyzed diastereo- and site-selective metal catalyzed *O*-allylation to furnish the pyran ring (Scheme 2.1). This approach was challenging due to the methods for intramolecular metal catalyzed allylic alkylation to form pyrans *via O*-allylation was limited. For instance, the 2,6-*cis*-disubstituted pyran formation, which catalyzed by palladium through allylic alkylation, gave poor selectivities to the corresponding trans-isomers.[7]

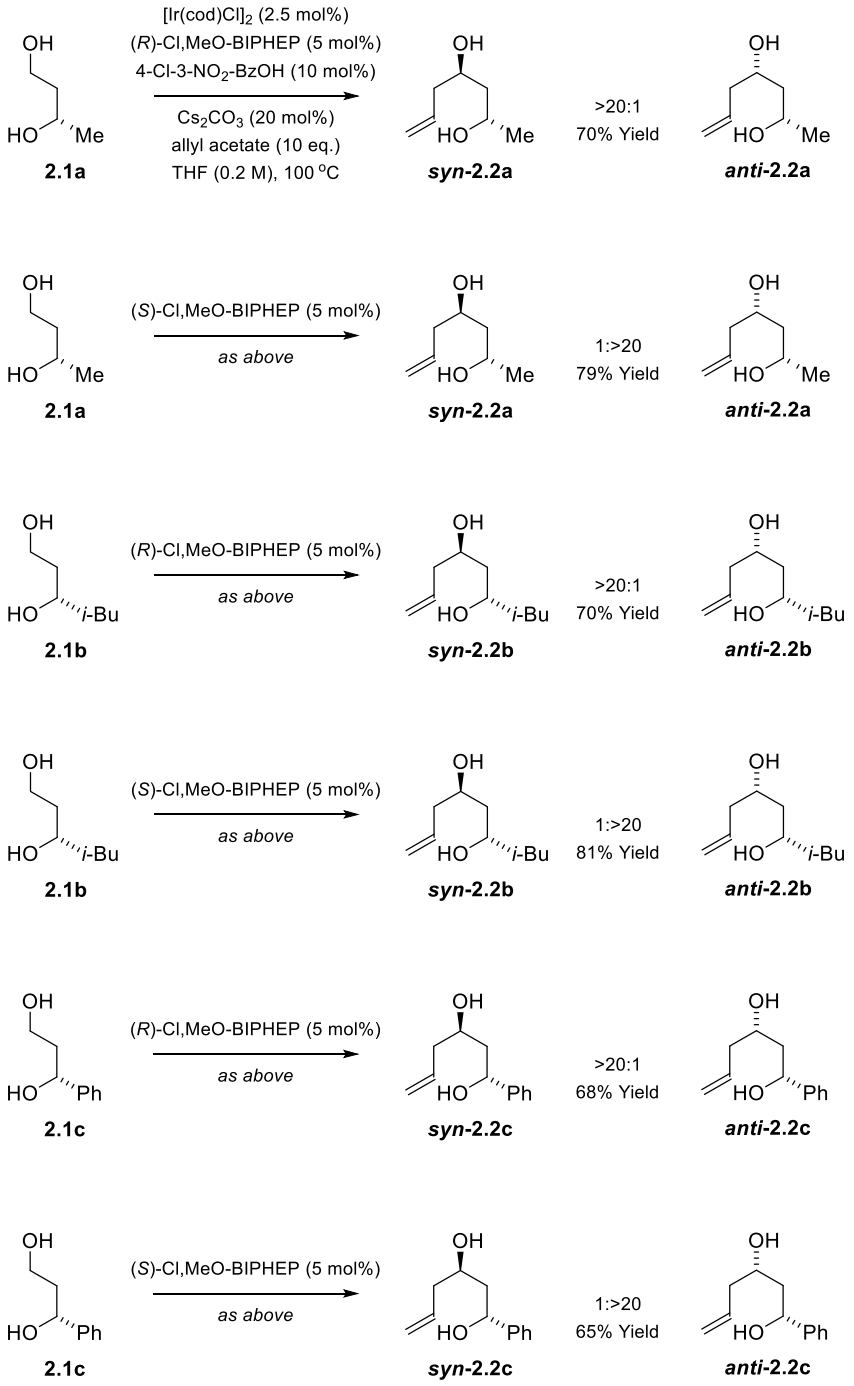
To identify an efficient catalyst for the diastereo- and site-selective *C*-allylation of chiral 1,3-diols, the commercial available diol **2.1a** was exposed to allyl acetate in the presence of $[Ir(cod)Cl]_2$, different 4-substituted-3-nitro-benzoic acids, and various axially chiral chelating phosphine ligands (selected results are showed in Scheme 2.2). It turned out that catalyst (*S*)-2-Ir-**Va**, which prepared from 4-chloro-3-nitro-benzoic acid and (*S*)-Cl,MeO-BIPHEP, gave the product *syn*-**2.2a** in 79% isolated yield as a single diastereomer, as determined by ^{1}H NMR analysis of the crude reaction mixture.



[a]Cited yields are of diastereomeric mixtures isolated by silica gel chromatography. Diastereomeric ratios were determined by 1H NMR analysis of crude reaction mixtures.

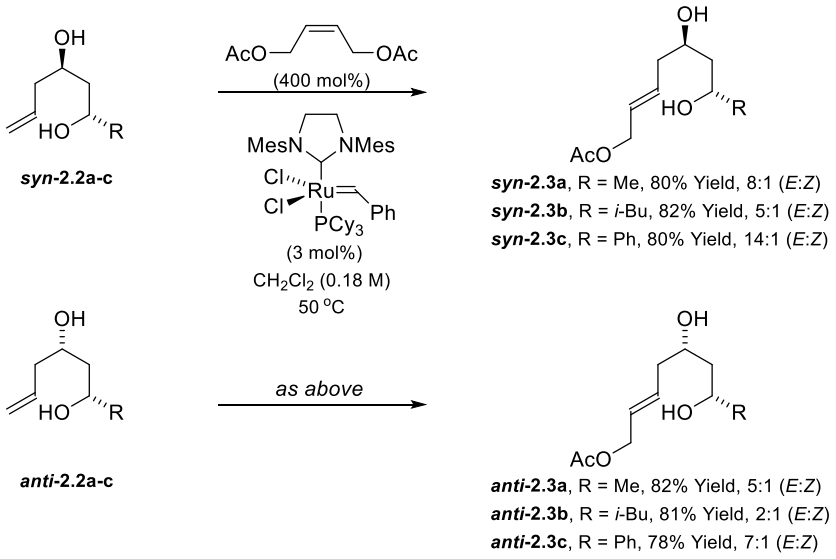
Scheme 2.2 Selected optimization experiments for *in situ* generation of iridium catalysts for the diastereo- and site-selective *C*-allylation of chiral 1,3-diol **2.1a**.[a]

Using the best condition showed in Scheme 2.2, the catalysts (*R*)- or (*S*)-2-Ir-**Va** were used to convert chiral 1,3-diols **2.1a**-**2.1c** to the diastereomeric products of *C*-allylation *syn*-**2.2a**, **2.2b**, **2.2c** and *anti*-**2.2a**, **2.2b**, **2.2c**, respectively (Scheme 2.3). In each case, good isolated yields and complete levels of catalyst-directed diastereoselectivity were observed.



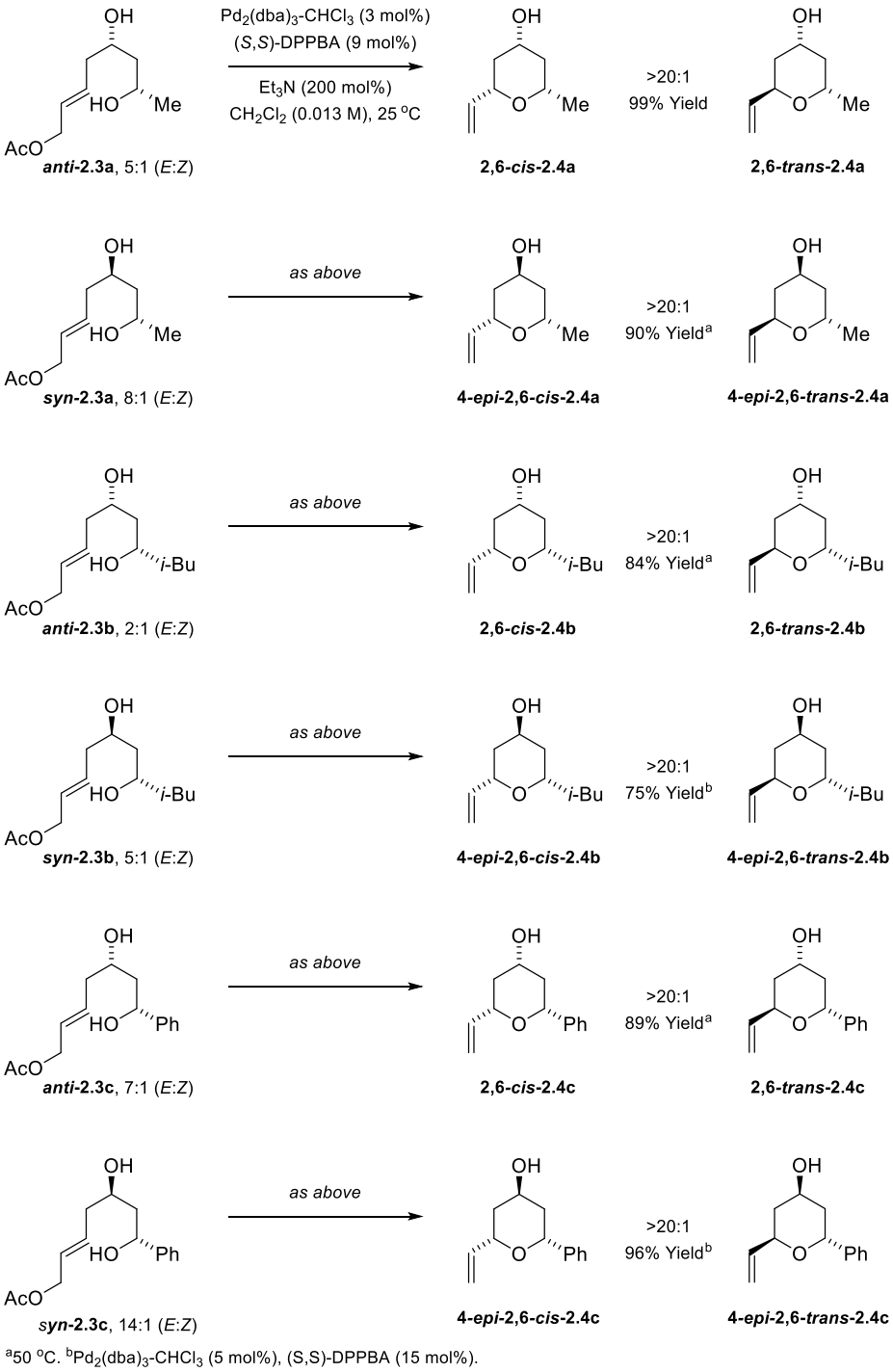
Scheme 2.3 Diastereo- and site-selective *C*-allylations of chiral 1,3-diols **2.1a**-**2.1c** catalyzed by iridium.

In the presence of *cis*-1,4-diacetoxy-2-butene and second generation Grubbs catalyst, the diastereomeric diols *syn*-**2.2a**, **2.2b**, **2.2c** and *anti*-**2.2a**, **2.2b**, **2.2c** were converted to the corresponding allylic acetates *syn*-**2.3a**, **2.3b**, **2.3c** and *anti*-**2.3a**, **2.3b**, **2.3c**. Although the unprotected 1,3-diol moieties evident in *syn*-**2.2a**, **2.2b**, **2.2c** and *anti*-**2.2a**, **2.2b**, **2.2c** produced some concerns regarding functional group compatibility, the desired allylic acetates *syn*-**2.3a**, **2.3b**, **2.3c** and *anti*-**2.3a**, **2.3b**, **2.3c** were obtained with excellent yield (up to 82%), albeit with incomplete control of alkene geometry (up to 14:1 *E*:*Z*, Scheme 2.4).[9]



Scheme 2.4 Cross-metathesis of chiral diols *syn*-**2.2a-c** and *anti*-**2.2a-c** to form allylic acetates *syn*-**2.3a-c** and *anti*-**2.3a-c**.

With the diastereomeric allylic acetates *syn*-**2.3a**, **2.3b**, **2.3c** and *anti*-**2.3a**, **2.3b**, **2.3c** in hand, which possessing the unprotected diol moieties, both 6-*endo* and 6-*exo*-*O*-allylation pathways are possible under the conditions of palladium catalyzed cyclization. The 2,6-*cis*-pyrans were formed selectively *via* 6-*exo*-*O*-allylation when we used an achiral palladium catalyst modified by 1,1'-bis(diphenylphosphino)ferrocene (dppf) although with incomplete levels of diastereoselectivity and in highly variable yields.



[a]50 °C. [b]$Pd_2(dba)_3$-$CHCl_3$ (5 mol%), (S,S)-DPPBA (15 mol%).

Scheme 2.5 Diastereo- and site-selective palladium catalyzed *O*-allylation reaction to form 4-hydroxy-2,6-*cis*-disubstituted tetrahydropyrans.

Next, to amplify the intrinsic stereochemical bias toward the 2,6-*cis*-diastereomers, a chiral palladium catalyst modified by (*S*,*S*)-1,2-diaminocyclohexane-*N*,*N*'-bis(2'-diphenylphosphinobenzoyl), DPPBA (Figure 2.2), were applied to catalyze this transformation (Scheme 2.5).[7b] The desired 4-hydroxy-2,6-*cis*-disubstituted pyrans 2,6-*cis*-**2.4a, 2.4b, 2.4c** and 4-*epi*-2,6-*cis*-**2.4a, 2.4b, 2.4c** were formed in excellent yield with complete levels of 2,6-*cis*-diastereoselectivity. These results reveal that pure olefin geometrical isomers are not required to achieve diastereoselective cyclization *via O*-allylation under the conditions of palladium catalysis due to rapid equilibration of the π-allyl haptomers with respect to cyclization.[10]

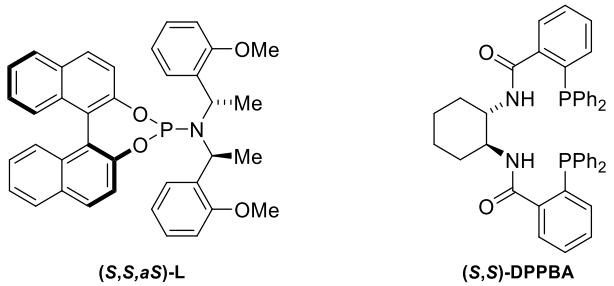
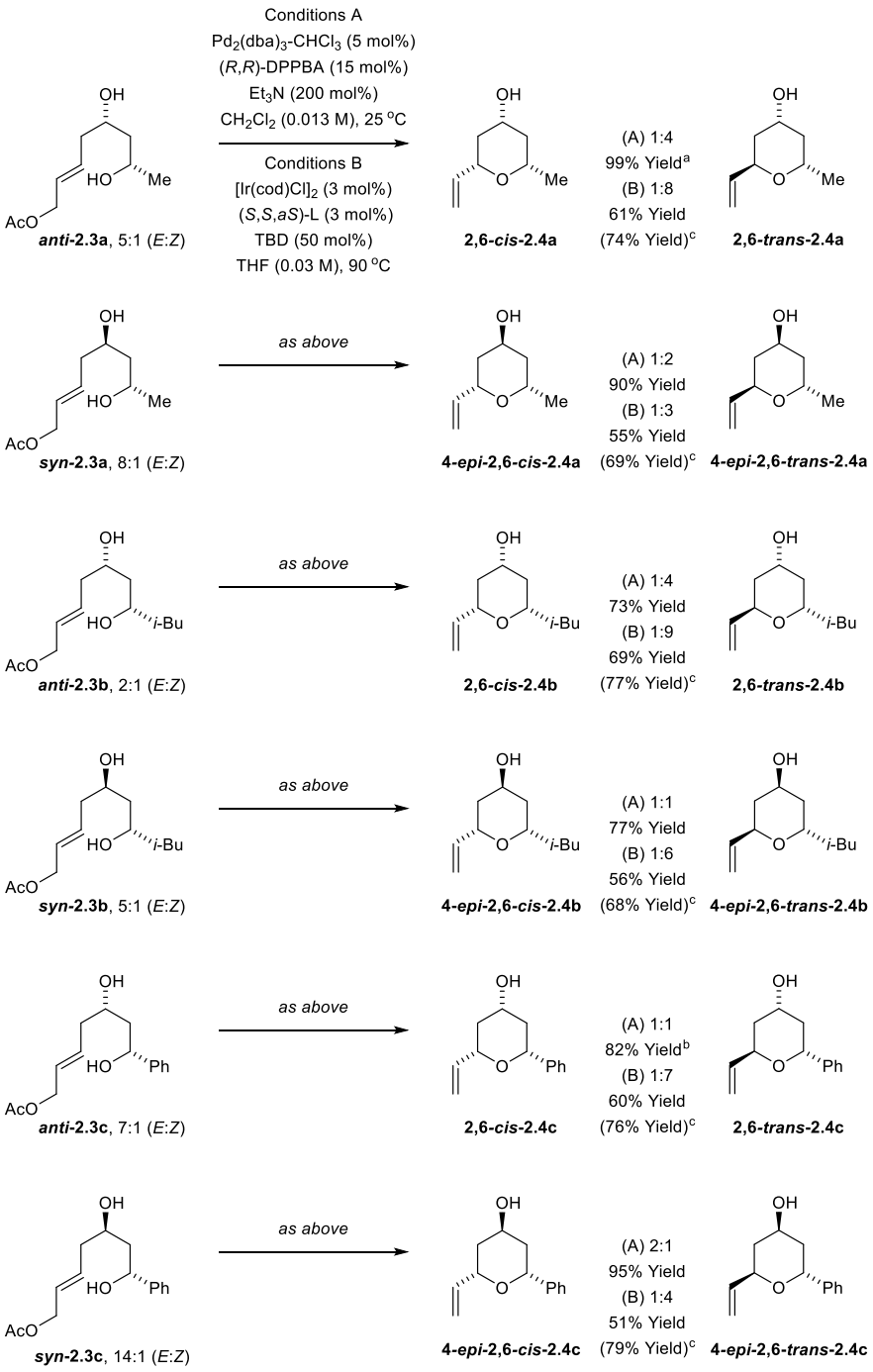


Figure 2.2 Structures of (*S*,*S*,*aS*)-L and (*S*,*S*)-DPPBA.

Preparation of the 4-hydroxy-2,6-*trans*-disubstituted pyrans was expected to be a far more formidable challenge, since the intrinsic bias of chiral 1,3-diols is to form the 2,6-*cis*-isomers. Palladium catalysts modified by diverse chiral phosphine ligands, including (*R*,*R*)-DPPBA, provided highly variable diastereoselectivities in the *O*-allylation of chiral 1,3-diols (Scheme 2.6). At best, using (*R*,*R*)-DPPBA as ligand, a 4:1 diastereoselectivity was observed in the *O*-allylation of the methyl-substituted diol *anti*-**2.3a** and the isobutyl-substituted diol *anti*-**2.3b**. However, for the remaining diols, use of palladium based catalysts modified by (*R*,*R*)-DPPBA led to relatively poor 2,6-*trans*-diastereoselectivities.

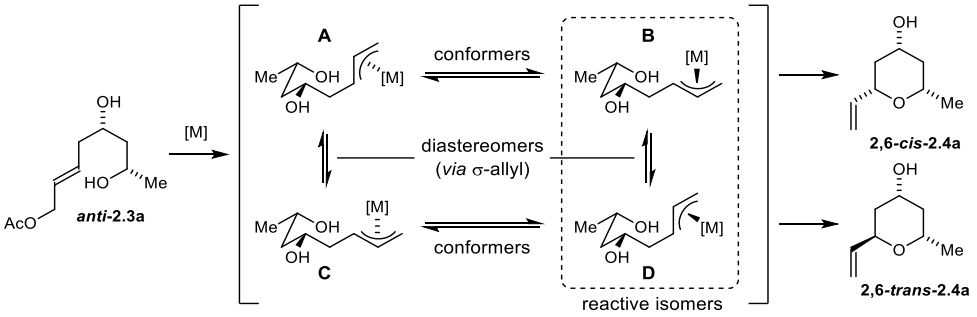


[a]$Pd_2(dba)_3$-$CHCl_3$ (3 mol%), (S,S)-DPPBA (9 mol%). [b]50 °C. [c]Yield based on recovered starting material.

Scheme 2.6 Diastereo- and site-selective Pd- and Ir-catalyzed *O*-allylation to form 4-hydroxy-2,6-*trans*-disubstituted tetrahydropyrans.

The Tsuji-Trost allylation of chiral 1,3-diols *syn*-**2.3a**, **2.3b**, **2.3c** and *anti*-**2.3a**, **2.3b**, **2.3c** was carried out using chiral iridium catalysts to improve the catalyst-directed diastereoselectivity (Scheme 2.6, conditions B).[11] After extensive reaction conditions screening to balance conversion and 2,6-*trans*-diastereoselectivity, we found that the cyclometalated iridium complex modified by the indicated chiral phosphoramidite ligand (*S*,*S*,*aS*)-L (Figure 2.2) provided optimal results. However, in several cases, incomplete conversion was observed, even though certain additives, such as tetrahydrothiophene, and triphenylphosphine with copper(I) iodide or Pb(II) acetate which were reported to enhance both stereoselectivity and conversion in such iridium catalyzed Tsuji-Trost allylations.[12]

2.3 Mechanism and Discussion



Scheme 2.7 Stereochemical features accounting for the trends in diastereoselectivity observed in the formation of 2,6-*cis*-**2.4a** and 2,6-*trans*-**2.4a** *via* Tsuji-Trost allylation.

To understand the trends in diastereoselectivity observed in the present cyclizations, a stereochemical model was provided to illustrate the cyclization process of *anti*-**2.3a** (Scheme 2.7). Rapid interconversion of the diastereomeric π-allyl intermediates **A**/**B** and **C**/**D** is anticipated.[10] For the diastereomers **A**/**B**, the reactive conformer **B** is *pseudo*-equatorially disposed, and cyclization occurs readily to furnish 2,6-*cis*-**2.4a**. For the

diastereomers **C**/**D**, the reactive conformer **D** is *pseudo*-axially disposed and, hence, the transition state for cyclization is anticipated to be higher in energy due to developing 1,3-diaxial interactions with the relatively large metal-bound vinyl moiety. Hence, reactions that form the 2,6-*cis*-diastereomers are intrinsically more facile.

2.4 CONCLUSION

A new strategy for protecting-group-free synthesis of 4-hydroxy-2,6-*cis*- or trans-tetrahydropyrans through successive nucleophilic and electrophilic allylations of chiral 1,3-diols **2.1a**-**2.1c** was developed. Using a cyclometalated iridium catalyst generated *in situ*, the redox-triggered *C*-allylation of chiral 1,3-diols **2.1a**-**2.1c** occurs with complete levels of catalyst-directed diastereoselectivity without using protecting groups to provide the chiral homoallylic diols **2.2a**-**2.2c**. In the presence of second-generation Grubbs catalyst, these homoallylic diols were converted to allylic acetates **2.3a**-**2.3c**, which were then undergo Tsuji-Trost cyclization to deliver the 4-hydroxy-2,6-*cis*- or trans-tetrahydropyrans. In the case of forming 4-hydroxy-2,6-*cis*-tetrahydropyrans, a chiral palladium catalyst gave complete levels of catalyst-directed diastereoselectivity. Meanwhile, upon using of chiral palladium or iridium catalysts, serviceble diastereoselectivityies could be obtained in the formation of 4-hydroxy-2,6-*trans*-tetrahydropyrans.

2.5 Experimental Details

General Information

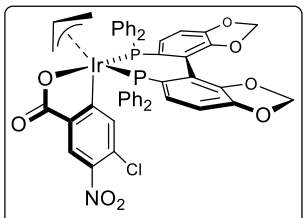
All reactions were run under an atmosphere of argon. Sealed tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator. Tetrahydrofuran, toluene, and dioxanes were distilled from sodium-benzophenone immediately prior to use. Dichloromethane was distilled from calcium hydride under a nitrogen atmosphere prior to use. Anhydrous solvents were transferred by oven-dried syringes. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F254). Visualization was accomplished with UV light followed by dipping in *p*-anisaldehyde stain solution then heating. Purification of reactions was carried out by flash chromatography using Silacycle silica gel (40-63 μm, unless indicated specifically). Potassium phosphate was purchased through Acros Organics, flame dried prior to use, and stored in a desiccator.

Spectroscopy, Spectrometry, and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). High-resolution mass spectra (HRMS) were obtained on an Agilent Technologies 6530 Accurate Mass Q-TOF LC/MS instrument and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M, M+H, or M-H), or a suitable fragment ion. ^{1}H nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δH (7.26 ppm). ^{13}C nuclear magnetic resonance spectra were recorded using a 100 MHz spectrometer for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CDCl_3$ δC (77.16 ppm).

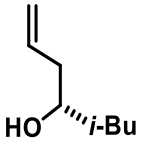
General Procedure for Ir-Catalyzed Allylation of Alcohols.

To a sealed tube under an argon atmosphere charged with alcohol (100 mol%), (*R*)-2-Ir-preformed catalyst (5.0 mol%), Cs_2CO_3 (100 mol%) and 4-Cl-3-NO_2-BzOH (10 mol%) was added freshly distilled THF (0.2 M), H_2O (500 mol%), and allyl acetate (200 mol%). The septum was quickly replaced with a screw cap and the reaction mixture was allowed to stir in an oil bath at 100 °C for 24 h. The reaction mixture was allowed to cool to ambient temperature, and was concentrated *in vacuo*. The residue was subjected to flash column chromatography to furnish title compound.



(*R*)-2-Ir-preformed catalyst

(*S*)-6-Methyl-1-hepten-4-ol (2-S-1).



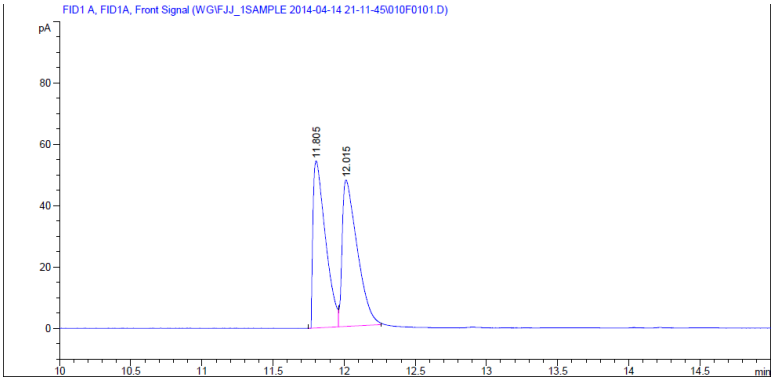
According to general procedure for Ir-catalyzed allylation of alcohols with 3-methylbutan-1-ol (44.1 mg, 0.50 mmol, 100 mol%), the product **2-S-1** was obtained as a colorless oil in 70% yield (45.0 mg, 0.35 mmol, *ee* = >99%) after flash column chromatography (hexanes/EtOAc = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00–5.67 (m, 1H), 5.28–4.98 (m, 2H), 3.87–3.57 (m, 1H), 2.36–2.21 (m, 1H), 2.20–2.05 (m, 1H), 1.88–1.71 (m, 1H), 1.55 (d, *J* = 4.1 Hz, 1H), 1.42 (ddd, *J* = 14.2, 8.8, 5.5 Hz, 1H), 1.25 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 118.2, 68.7, 46.1, 42.6, 24.7, 23.5, 22.2.

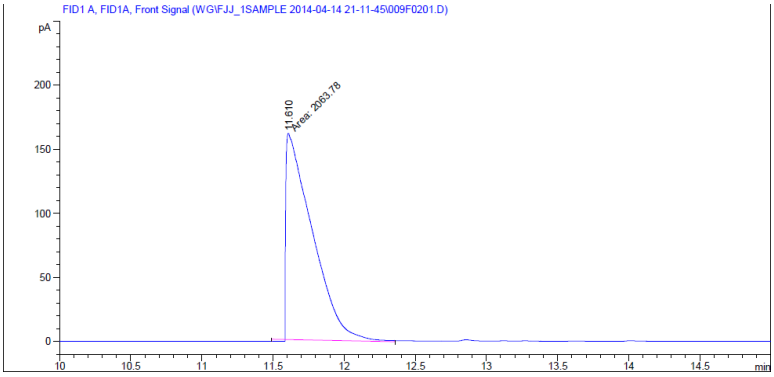
$[\alpha]^{25}_D$ = –31.78 ° (c = 1.50, $CHCl_3$).

Data is consistent with that reported in the literature.[13]



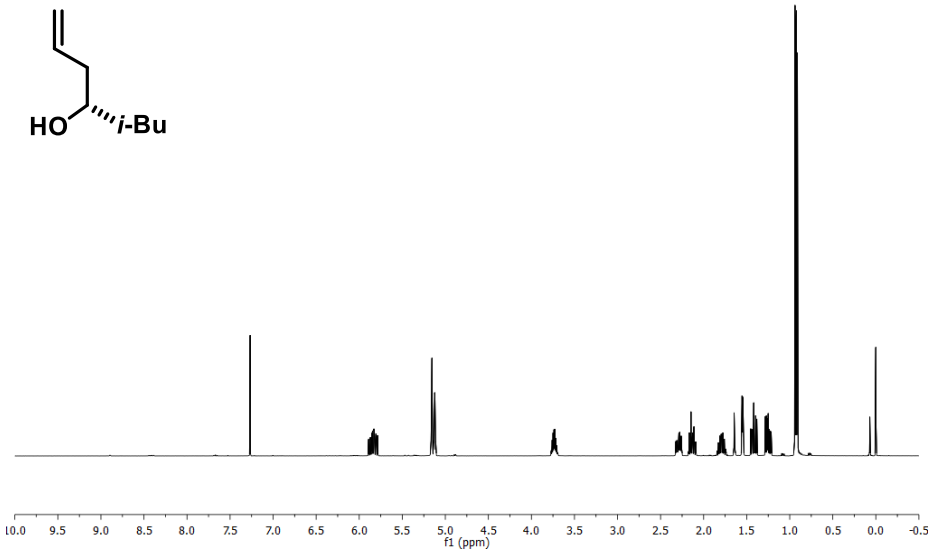
Signal 1: FID1 A, FID1A, Front Signal

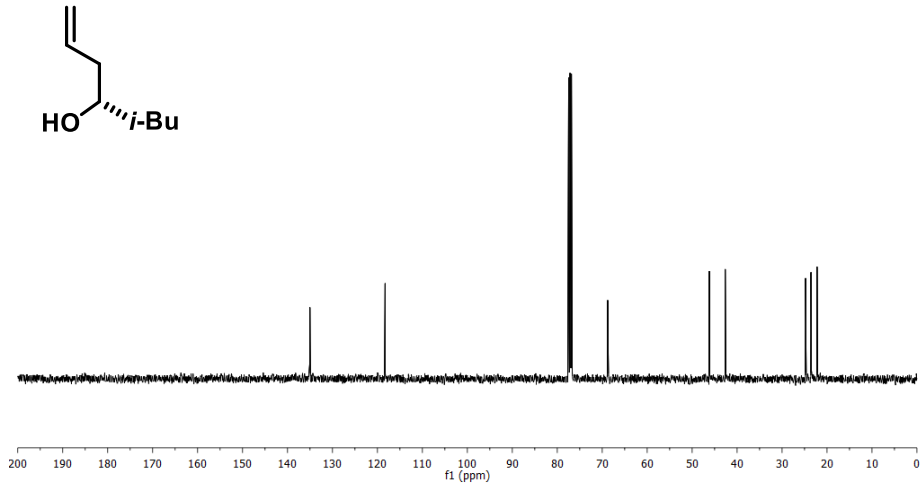
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	11.805	BV	0.0884	330.29260	54.40679	48.52126
2	12.015	VB	0.1042	350.42462	47.64088	51.47874
Totals :				680.71722	102.04767	



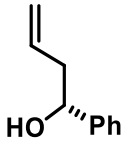
Signal 1: FID1 A, FID1A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	11.610	MM	0.2140	2063.78369	160.75916	1.000e2
Totals :				2063.78369	160.75916	


HO
i-Bu
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


HO
i-Bu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(*R*)-1-Phenylbut-3-en-1-ol (2-S-2).



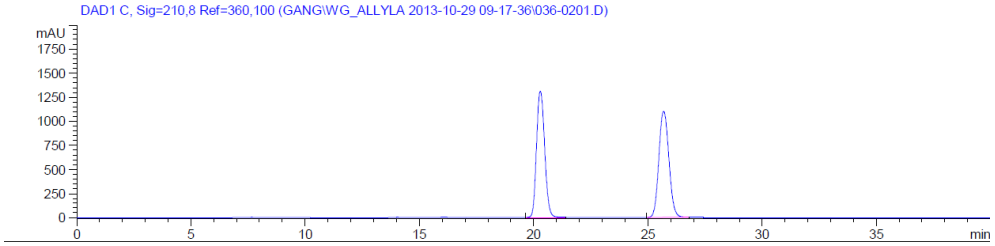
According to general procedure for Ir-catalyzed allylation of alcohols with benzyl alcohol (59.0 mg, 0.54 mmol, 100 mol%), the product **2-S-2** was obtained as a colorless oil in 75% yield (64.0 mg, 0.41 mmol, *ee* = 94%) after flash column chromatography (hexanes/EtOAc = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 4H), 7.31–7.23 (m, 1H), 5.86–5.74 (m, 1H), 5.31–5.03 (m, 2H), 4.72 (m, 1H), 2.47–2.43 (m, 2H), 2.11 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 134.5, 128.5, 127.6, 125.9, 118.5, 73.4, 43.9.

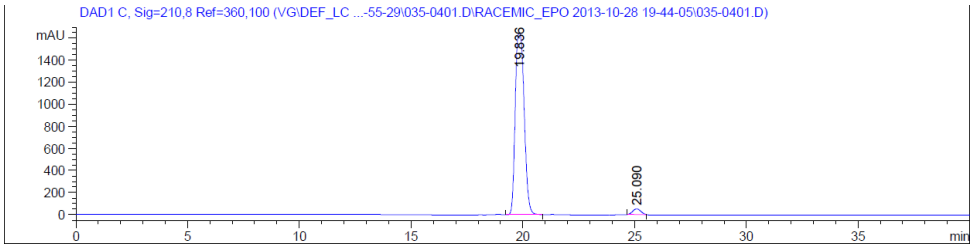
$[\alpha]^{25}_D$ = +60.33° (c = 2.00, $CHCl_3$).

Data is consistent with that reported in the literature.[14]



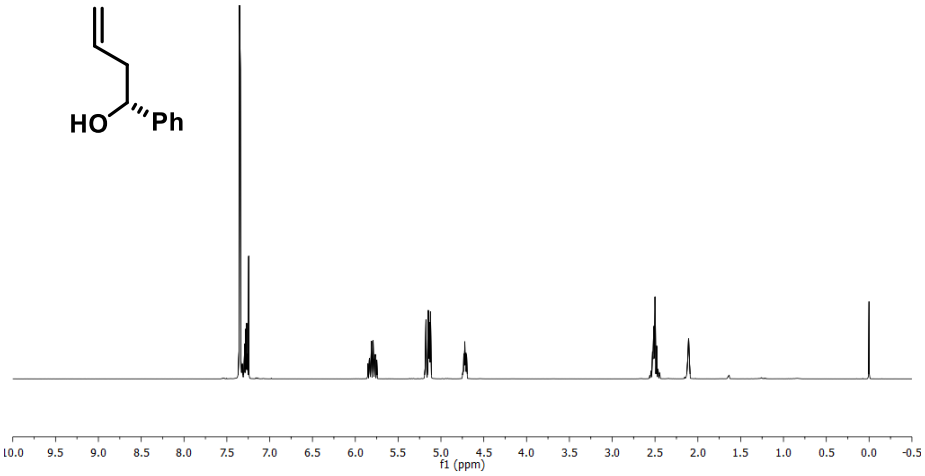
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

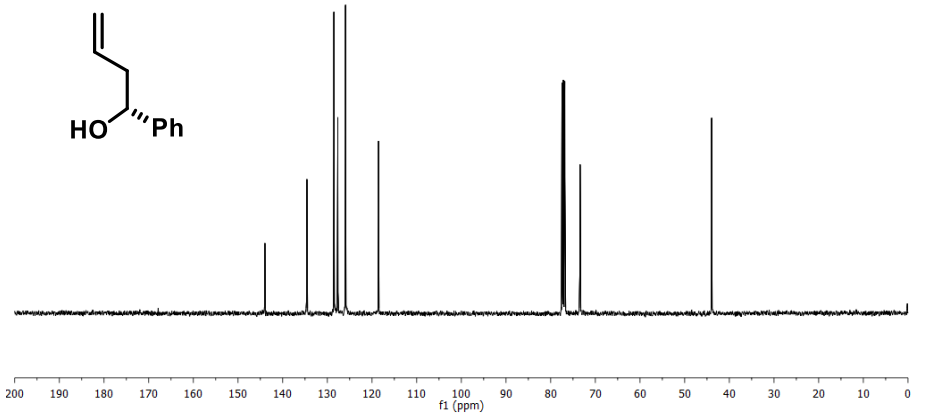
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.290	BB	0.3932	3.24477e4	1308.86548	49.0957
2	25.687	BB	0.4826	3.36430e4	1100.71118	50.9043
Totals :				6.60907e4	2409.57666	



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.836	VB	0.4451	4.56689e4	1649.11511	97.2821
2	25.090	MM	0.4206	1275.91785	50.56445	2.7179
Totals :				4.69448e4	1699.67956	

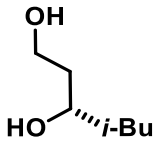

HO
Ph
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


HO
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

General Procedure for Preparation of 1,3-Diols.

To a flask charged with allylic alcohol (100 mol%) was added freshly distilled CH_2Cl_2 (0.1 M). Ozone was bubbled through the solution for 15 min at –78 °C, at which point sodium borohydride ($NaBH_4$, 500 mol%) was added to the solution. The reaction mixture was gradually warmed to ambient temperature and stirred overnight. Saturated NH_4Cl solution was added at 0 °C to quench the reaction. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was subjected to flash column chromatography to furnish the title compound.

(*S*)-5-Methylhexane-1,3-diol (2.1b).



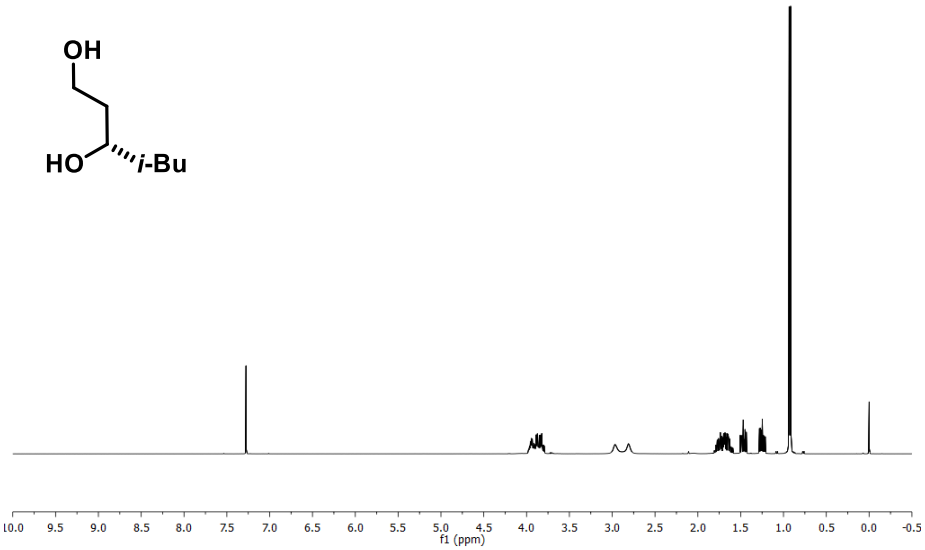
According to general procedure for preparation of 1,3-diols with (*S*)-6-methyl-1-hepten-4-ol (869.1 mg, 6.79 mmol, 100 mol%), the product **2.1b** was obtained as a colorless oil in 85% yield (763.0 mg, 5.77 mmol, *ee* = >99%) after flash column chromatography (CH_2Cl_2/MeOH = 20:1).

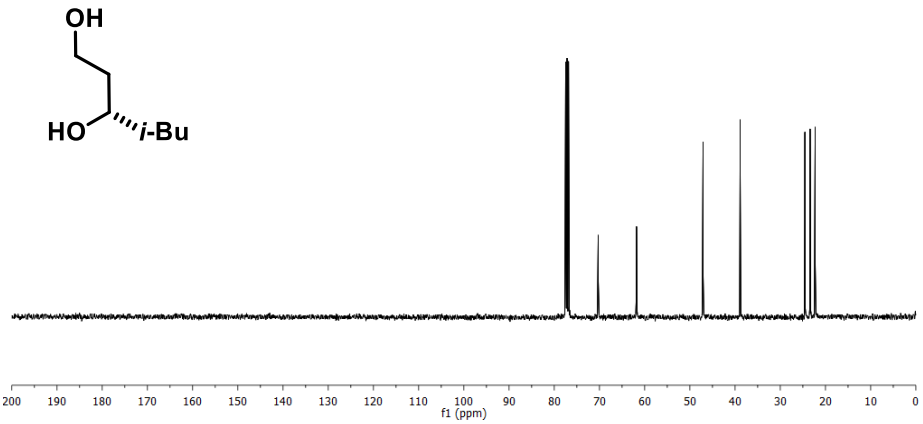
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05–3.71 (m, 3H), 2.97 (br s, 1H), 2.81 (br s, 1H), 1.85–1.56 (m, 3H), 1.53–1.41 (m, 1H), 1.31–1.18 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 70.2, 61.8, 47.0, 38.8, 24.5, 23.4, 22.2.

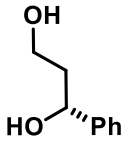
$[\alpha]^{25}_D$ = –20.67 ° (c = 1.00, $CHCl_3$).

Data is consistent with that reported in the literature.[15]


OH
HO
i-Bu
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
i-Bu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(*R*)-1-Phenylpropane-1,3-diol (2.1c).



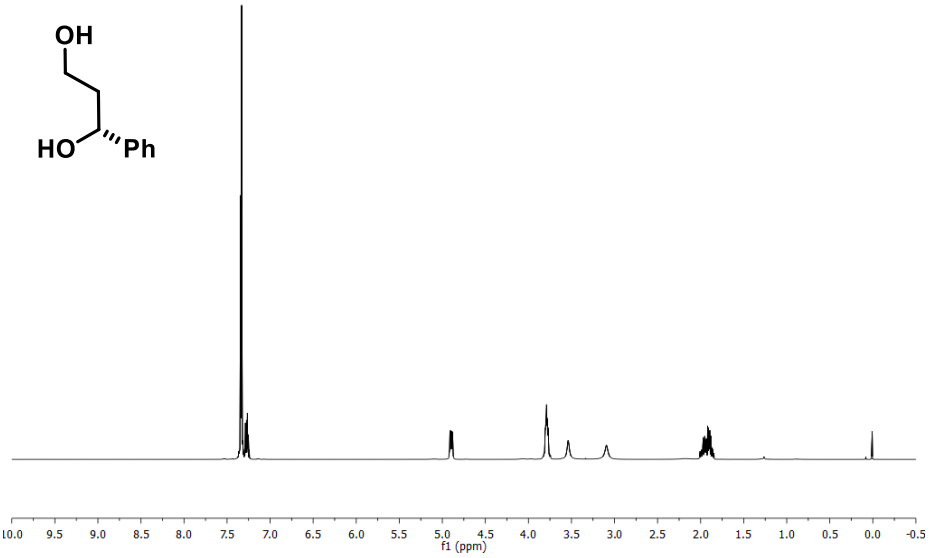
According to general procedure for preparation of 1,3-diols with (*R*)-1-phenylbut-3-en-1-ol (741.0 mg, 5.0 mmol, 100 mol%), the product **2.1c** was obtained as a colorless oil in 75% yield (580 mg, 3.75 mmol, *ee* = 94%) after flash column chromatography (CH_2Cl_2/MeOH = 20:1).

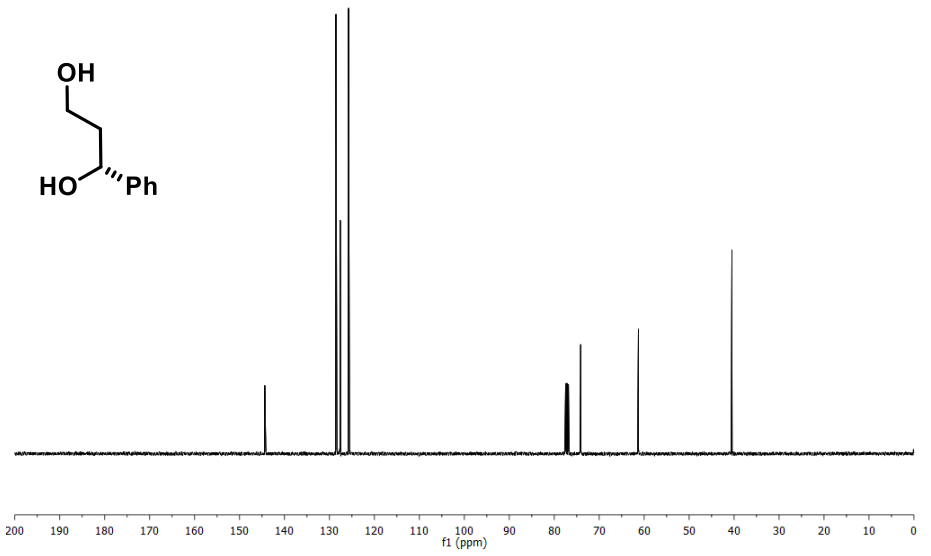
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 4H), 7.29–7.23 (m, 1H), 4.89 (dd, *J* = 8.7, 3.8 Hz, 1H), 3.96–3.66 (m, 2H), 3.59 (br s, 1H), 3.09 (br s, 1H), 2.08–1.74 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 128.5, 127.6, 125.7, 74.1, 61.2, 40.4.

$[\alpha]^{25}_D$ = +42.50 ° (c = 0.40, $CHCl_3$).

Data is consistent with that reported in the literature.[16]

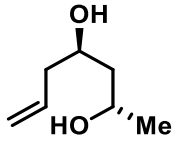

OH
HO
Ph
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

General Procedure for Ir-Catalyzed Allylation of 1,3-Diols.

To a sealed tube under an argon atmosphere charged with 1,3-diol (100 mol%), $[Ir(cod)Cl]_2$ (2.5 mol%), (*S*)- or (*R*)-Cl, MeO-BIPHEP (5 mol%), Cs_2CO_3 (20 mol%) and 4-Cl-3-NO_2-BzOH (10 mol%) was added freshly distilled THF (0.2 M) and allyl acetate (10 eq.). The septum was quickly replaced with a screw cap and the reaction mixture was allowed to stir in an oil bath at 100 °C for 40 h. The reaction mixture was allowed to cool to ambient temperature, and was concentrated *in vacuo*. The residue was subjected to flash column chromatography to furnish title compound.

(2*S*,4*R*)-Hept-6-ene-2,4-diol (*syn*-2.2a).



According to general procedure for Ir-catalyzed allylation of 1,3-diols with (*S*)-butane-1,3-diol **2.1a** (18 mg, 0.20 mmol, 100 mol%) and (*R*)-Cl, MeO-BIPHEP, the product ***syn*-2.2a** was obtained as a light yellow oil in 70% yield (18.3 mg, 0.14 mmol, *dr* = >20:1) after flash column chromatography (hexanes/EtOAc = 1:1).

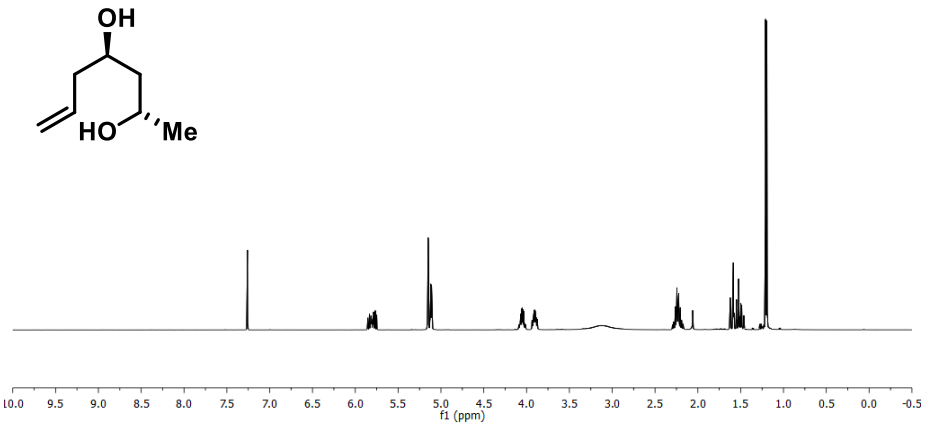
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.73 (m, 1H), 5.18–5.13 (m, 1H), 5.13–5.09 (m, 1H), 4.11–3.99 (m, 1H), 3.95–3.83 (m, 1H), 3.13 (br s, 2H), 2.31–2.15 (m, 2H), 1.65–1.45 (m, 2H), 1.20 (d, J = 6.2 Hz, 3H).

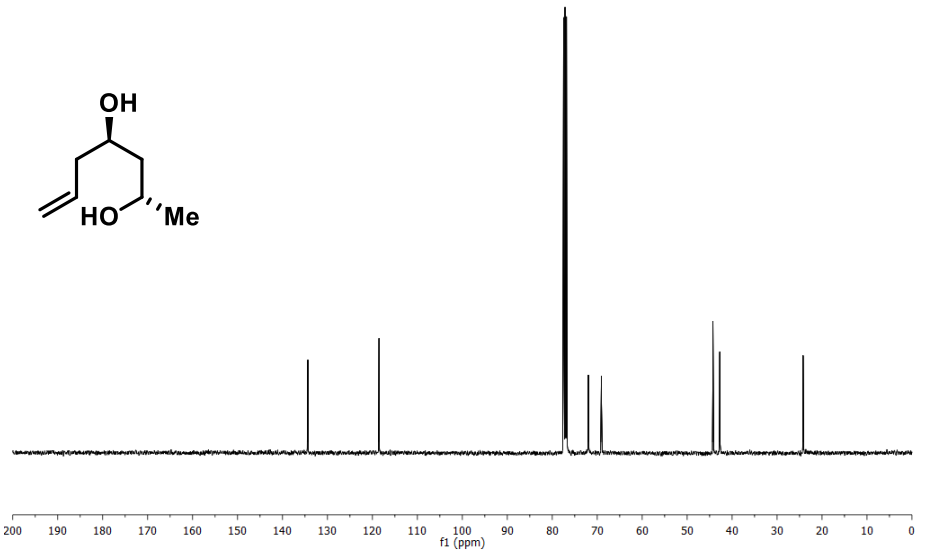
^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 118.4, 71.8, 68.9, 44.1, 42.6, 24.1.

IR (neat) 3329, 2969, 2933, 1433, 1324, 1087, 914 cm^{-1}.

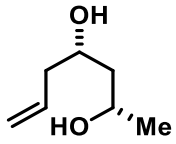
LRMS (CI+) calcd. for $C_7H_{15}O_2$ $[M+H]^+$ 131, found 131.

$[\alpha]^{25}_D$ = +2.0 ° (c = 0.50, $CHCl_3$).


OH
HO
Me
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*S*,4*S*)-Hept-6-ene-2,4-diol (*anti*-2.2a).



According to general procedure for Ir-catalyzed allylation of 1,3-diols with (*S*)-butane-1,3-diol **2.1a** (18 mg, 0.20 mmol, 100 mol%) and (*S*)-Cl, MeO-BIPHEP, the product ***anti*-2.2a** was obtained as a light yellow oil in 79% yield (20.6 mg, 0.16 mmol, *dr* = 1:>20) after flash column chromatography (hexanes/EtOAc = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29–5.75 (m, 1H), 5.18–5.13 (m, 1H), 5.13–5.08 (m, 1H), 4.23–4.08 (m, 1H), 4.04–3.93 (m, 1H), 2.75 (br s, 2H), 2.30–2.21 (m, 2H), 1.62–1.57 (m, 2H), 1.22 (d, J = 6.2 Hz, 3H).

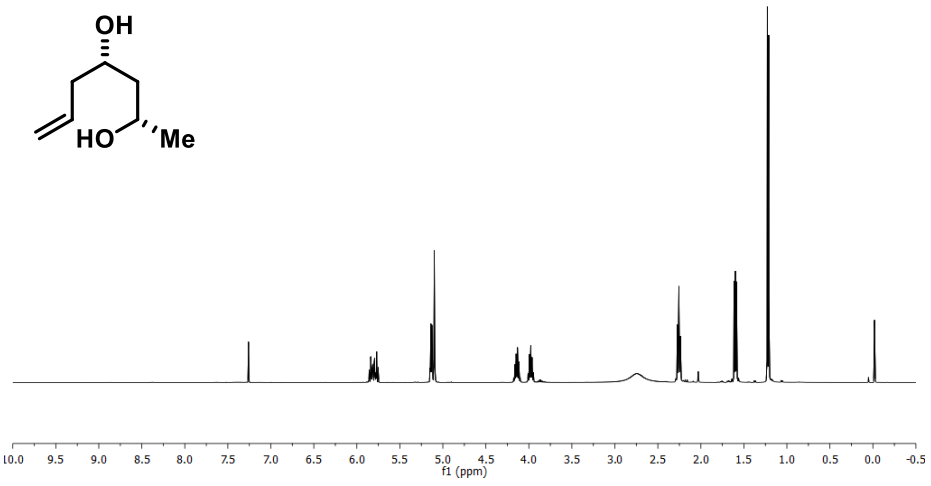
^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 118.2, 68.3, 65.4, 43.7, 42.1, 23.6.

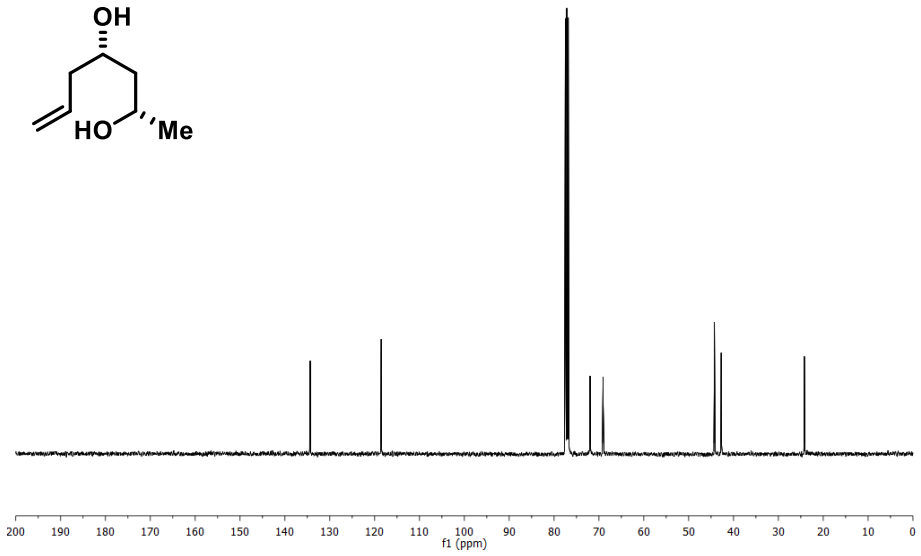
IR (neat) 3356, 2967, 2933, 1433, 1414, 1374, 1087, 996 cm^{-1}.

LRMS (CI+) calcd. for $C_7H_{15}O_2$ $[M+H]^+$ 131, found 131.

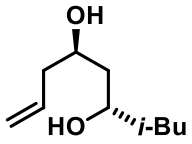
$[\alpha]^{25}_D$ = +22.4 ° (c = 0.61, $CHCl_3$).

Data is consistent with that reported in the literature.[17]


OH
HO
Me
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(4*R*,6*S*)-8-Methylnon-1-ene-4,6-diol (*syn*-2.2b).



According to general procedure for Ir-catalyzed allylation of 1,3-diols with (*S*)-5-methylhexane-1,3-diol **2.1b** (26.5 mg, 0.20 mmol, 100 mol%) and (*R*)-Cl, MeO-BIPHEP, the product ***syn*-2.2b** was obtained as a light yellow oil in 70% yield (24 mg, 0.14 mmol, *dr* = >20:1) after flash column chromatography (hexanes/EtOAc = 4:1).

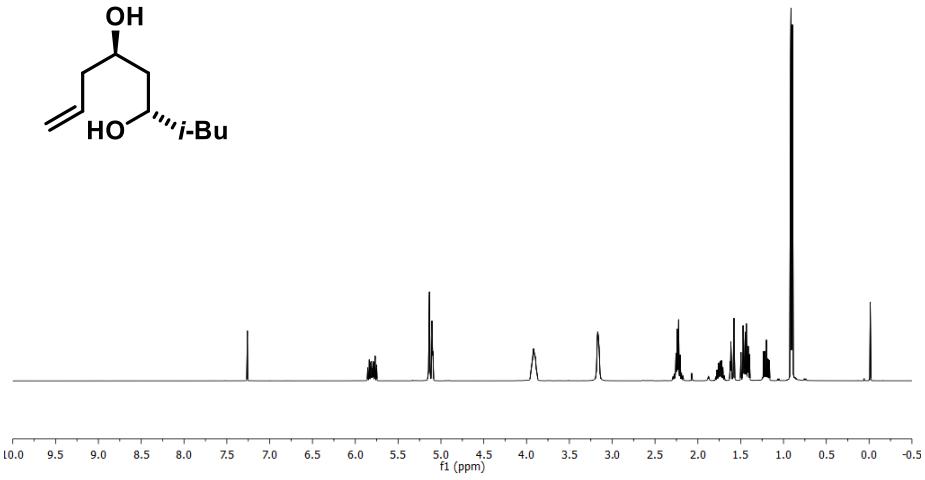
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98–5.64 (m, 1H), 5.18–5.09 (m, 2H), 4.00–3.86 (m, 2H), 3.17 (s, 2H), 2.34-2.15 (m, 2H), 1.84–1.68 (m, 1H), 1.67–1.55 (m, 1H), 1.54–1.37 (m, 2H), 1.29–1.13 (m, 1H), 0.93 (d, *J* = 1.6 Hz, 3H), 0.91 (d, *J* = 1.6 Hz, 3H).

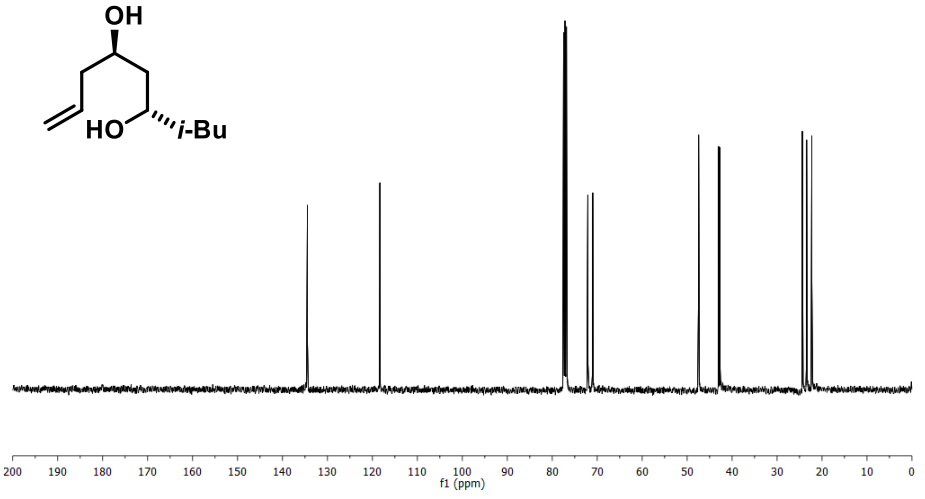
^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 118.3, 72.1, 71.0, 47.4, 43.0, 42.7, 24.4, 23.4, 22.3.

IR (neat) 3331, 2954, 2932, 1434, 1081, 914 cm^{-1}.

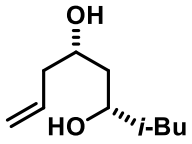
LRMS (ESI+) calcd. for $C_{10}H_{20}O_2Na$ $[M+Na]^+$ 195, found 195.

$[\alpha]^{25}_D$ = –10.33 ° (c = 1.00, $CHCl_3$).


OH
HO
i-Bu
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
i-Bu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(4*S*,6*S*)-8-Methylnon-1-ene-4,6-diol (*anti*-2.2b).



According to general procedure for Ir-catalyzed allylation of 1,3-diols with (*S*)-5-methylhexane-1,3-diol **2.1b** (26.5 mg, 0.20 mmol, 100 mol%) and (*S*)-Cl, MeO-BIPHEP, the product ***anti*-2.2b** was obtained as a light yellow oil in 81% yield (28 mg, 0.16 mmol, *dr* = 1: >20) after flash column chromatography (hexanes/EtOAc = 4:1).

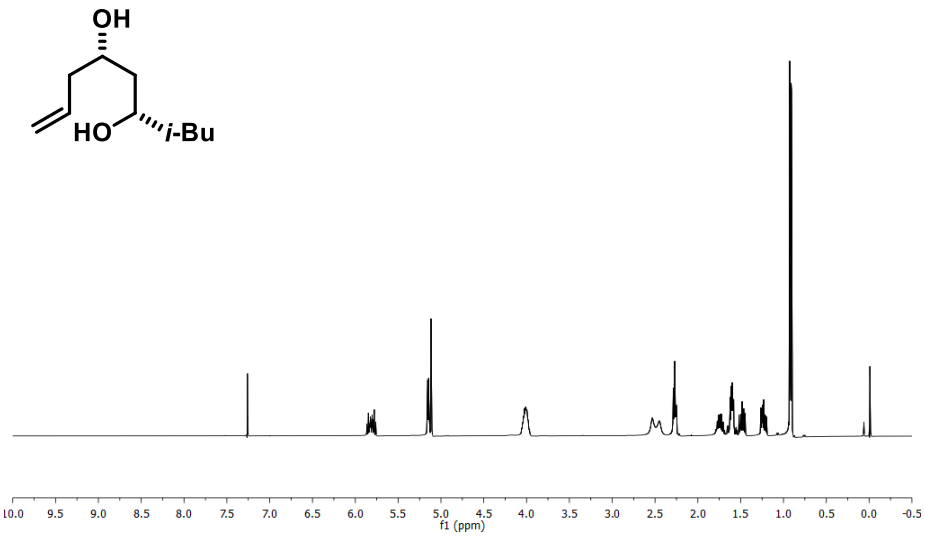
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96–5.66 (m, 1H), 5.19–5.14 (m, 1H), 5.14–5.10 (m, 1H), 4.18–3.86 (m, 2H), 2.54 (br s, 1H), 2.46 (br s, 1H), 2.36–2.16 (m, 2H), 1.85–1.68 (m, 1H), 1.68–1.54 (m, 2H), 1.54–1.41 (m, 1H), 1.35–1.16 (m, 1H), 0.92 (d, *J* = 1.7 Hz, 3H), 0.90 (d, *J* = 1.7 Hz, 3H).

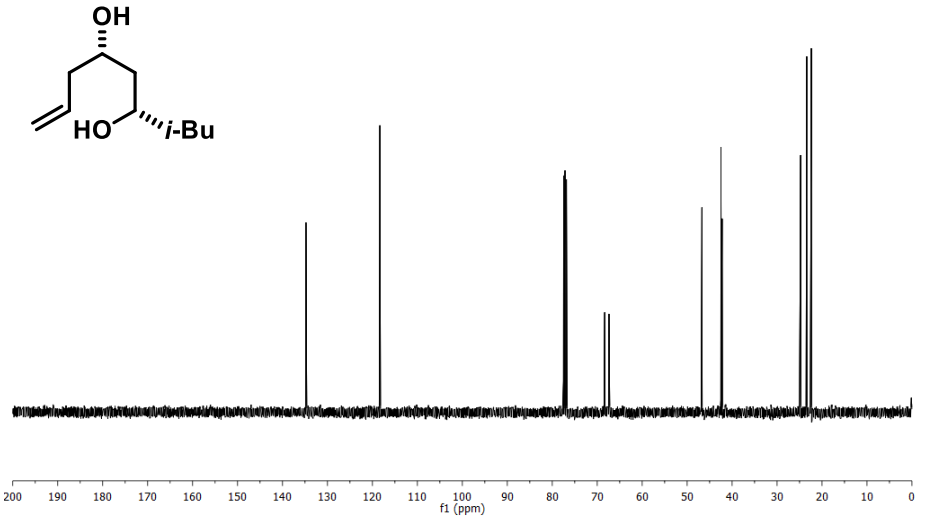
^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 118.3, 68.3, 67.4, 46.7, 42.5, 42.2, 24.8, 23.4, 22.4.

IR (neat) 3355, 2954, 2933, 1433, 1139, 1049, 913 cm^{-1}.

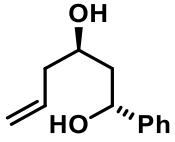
LRMS (ESI+) calcd. for $C_{10}H_{20}O_2Na$ $[M+Na]^+$ 195, found 195.

$[\alpha]^{25}_D$ = +16.33 ° (c = 1.00, $CHCl_3$).


OH
HO
i-Bu
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
i-Bu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(1*R*,3*R*)-1-Phenylhex-5-ene-1,3-diol (*syn*-2.2c).



According to general procedure for Ir-catalyzed allylation of 1,3-diols with (*R*)-1-phenylpropane-1,3-diol **2.1c** (30 mg, 0.20 mmol, 100 mol%) and (*R*)-Cl, MeO-BIPHEP, the product ***syn*-2.2c** was obtained as a light yellow solid in 68% yield (26 mg, 0.14 mmol, *dr* = >20:1) after flash column chromatography (hexanes/EtOAc = 4:1).

mp: 61.2–62.5 °C.

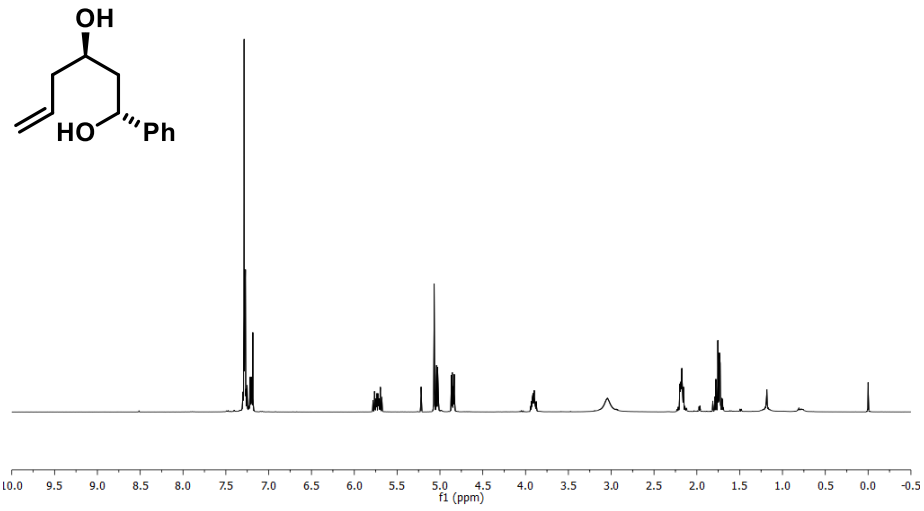
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.07 (m, 5H), 5.87–5.58 (m, 1H), 5.09–5.00 (m, 2H), 4.85 (dd, *J* = 8.9, 4.1 Hz, 1H), 3.98–3.83 (m, 1H), 3.04 (br s, 2H), 2.28–2.07 (m, 2H), 1.88–1.62 (m, 2H).

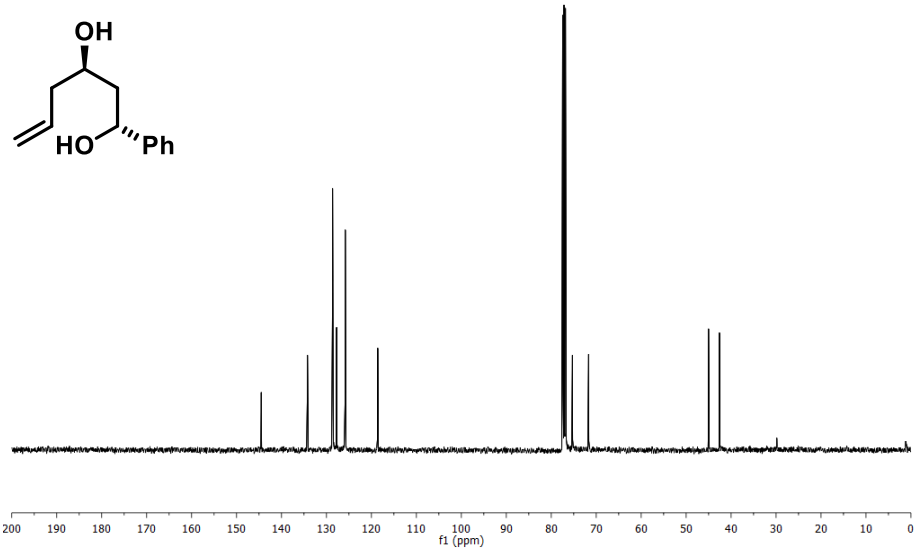
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 134.2, 128.6, 127.7, 125.8, 118.6, 75.3, 71.7, 45.0, 42.6.

IR (neat) 3288, 2940, 2914, 1436, 1330, 1025, 917 cm^{-1}.

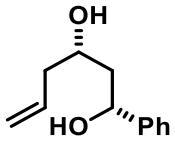
LRMS (ESI+) calcd. for $C_{12}H_{16}O_2Na$ $[M+Na]^+$ 215, found 215.

$[\alpha]^{25}_D$ = +17.50 ° (c = 0.40, $CHCl_3$).


OH
HO
Ph
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(*1R,3R*)-1-Phenylhex-5-ene-1,3-diol (*anti*-2.2c).



According to general procedure for Ir-catalyzed allylation of 1,3-diols with (*R*)-1-phenylpropane-1,3-diol **2.1c** (30 mg, 0.20 mmol, 100 mol%) and (*S*)-Cl, MeO-BIPHEP, the product ***anti*-2.2c** was obtained as a light yellow solid in 65% yield (25 mg, 0.13 mmol, *dr* = 1:>20) after flash column chromatography (hexanes/EtOAc = 4:1).

mp: 61.6–62.8 °C.

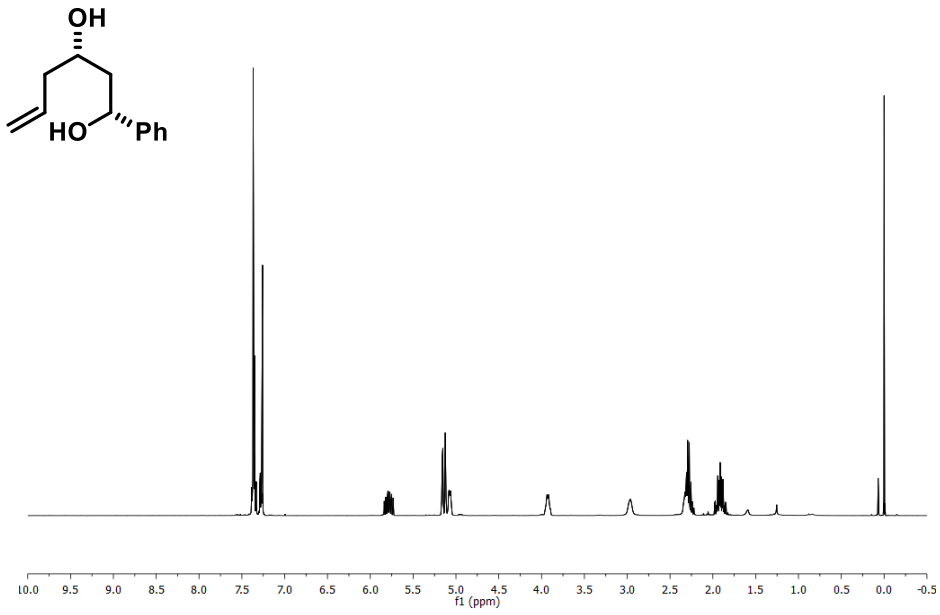
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.00 (m, 5H), 5.86–5.50 (m, 1H), 5.10–5.01 (m, 2H), 4.98 (dd, *J* = 7.9, 3.5 Hz, 1H), 3.95–3.72 (m, 1H), 2.71 (br s, 2H), 2.32–2.07 (m, 2H), 1.92–1.69 (m, 2H).

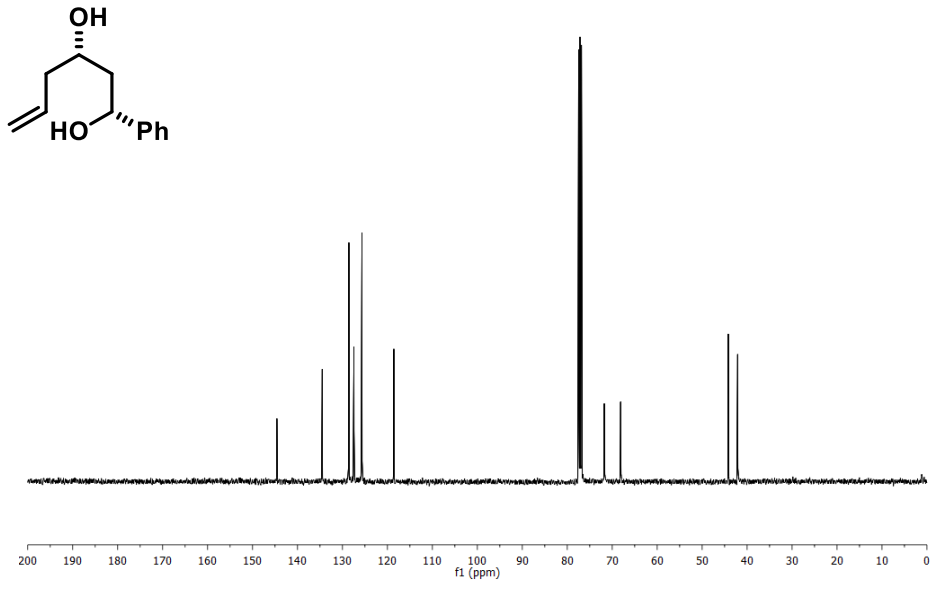
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 134.5, 128.6, 127.5, 125.7, 118.6, 71.8, 68.1, 44.2, 42.1.

IR (neat) 3371, 2912, 1452, 1431, 1335, 1052, 915 cm^{-1}.

LRMS (ESI+) calcd. for $C_{12}H_{16}O_2Na$ $[M+Na]^+$ 215, found 215.

$[\alpha]^{25}_D$ = +61.67 ° (c = 1.00, $CHCl_3$).

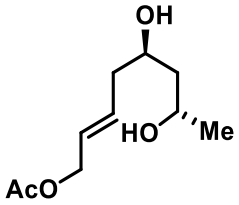

OH
HO
Ph
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

General Procedure for Cross Metathesis.

To a sealed tube under an argon atmosphere charged with diol **2.2** (100 mol%) and *cis*-1,4-diacetoxy-2-butene (400 mol%) was added freshly distilled CH_2Cl_2 (0.18 M). The Grubbs second generation catalyst [$Cl_2(PCy_3)$(IMes)Ru=CHPh] (3 mol%) was added in one portion. Tthe septum was quickly replaced with a screw cap, and the reaction mixture was allowed to stir in an oil bath at 50 °C for 20 h. The reaction mixture was allowed to cool to ambient temperature, was concentrated *in vacuo*. The residue was subjected to flash column chromatography to furnish title product.

(5*R*,7*S*,*E*)-5,7-Dihydroxyoct-2-en-1-yl Acetate (*syn*-2.3a).



According to general procedure for cross metathesis with ***syn*-2.2a** (230 mg, 1.77 mmol, 100 mol%), the product ***syn*-2.3a** was obtained as a brown oil in 80% yield (288 mg, 1.42 mmol, *E*:*Z* = 8:1) after flash column chromatography (hexanes/EtOAc = 2:1 to 1:1).

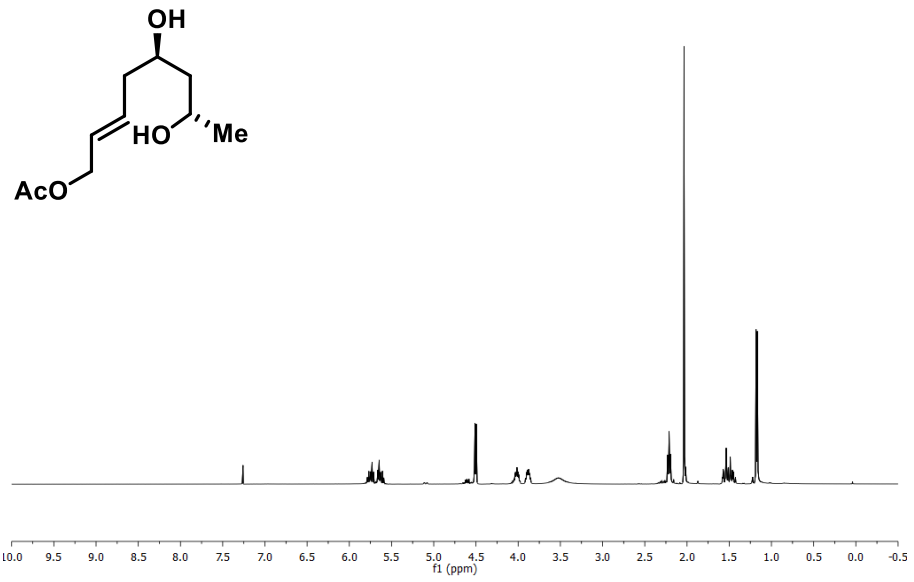
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82–5.55 (m, 2H), 4.50 (dd, *J* = 6.2, 0.7 Hz, 2H), 4.09–3.96 (m, 1H), 3.93–3.83 (m, 1H), 3.52 (br s, 2H), 2.21 (dd, *J* = 6.4, 6.4 Hz, 2H), 2.03 (s, 3H), 1.59–1.41 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 3H).

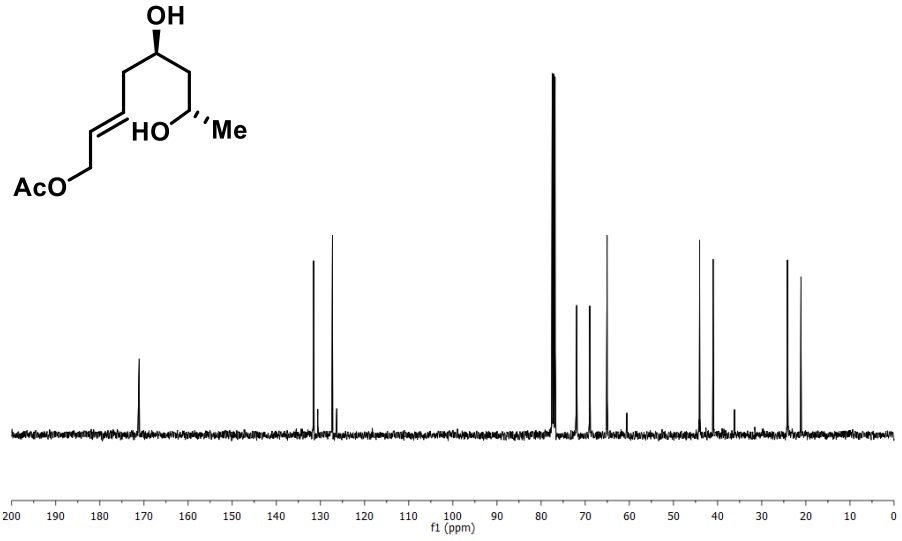
^{13}C NMR (100 MHz, $CDCl_3$, mixture of *E*- and *Z* isomers) δ 171.3, 171.1, 131.5, 130.6, 127.3, 126.3, 71.9, 69.0, 65.0, 60.5, 44.2, 44.1, 41.0, 36.2, 24.2, 21.2.

IR (neat) 3364, 2934, 1736, 1230, 1024, 966 cm^{-1}.

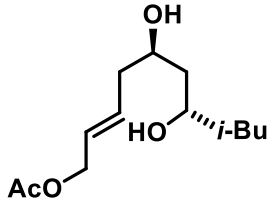
LRMS (ES+) calcd. for $C_{10}H_{19}O_4$ $[M+H]^+$ 203, found 203.

$[\alpha]^{25}_D$ = +8.06 ° (c = 0.62, $CHCl_3$).


OH
HO
Me
AcO
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
Me
AcO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(5*R*,7*S*,*E*)-5,7-Dihydroxy-9-methyldec-2-en-1-yl Acetate (*syn*-2.3b).



According to general procedure for cross metathesis with ***syn*-2.2b** (80 mg, 0.46 mmol, 100 mol%), the product ***syn*-2.3b** was obtained as a brown oil in 82% yield (93 mg, 0.38 mmol, *E*:*Z* = 5:1) after flash column chromatography (hexanes/EtOAc = 3:1 to 2:1).

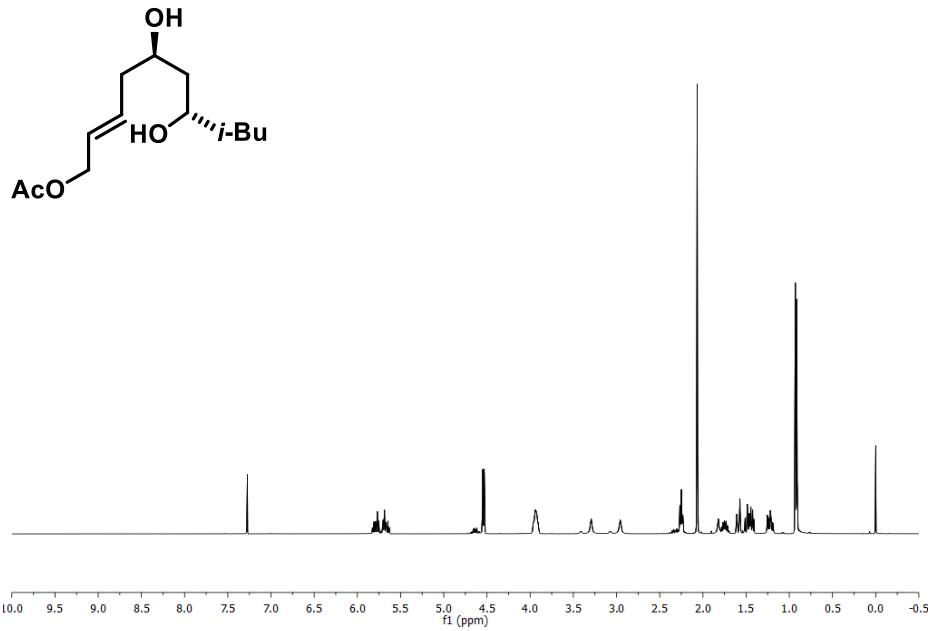
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85–5.60 (m, 2H), 4.54 (d, *J* = 6.1 Hz, 2H), 4.01–3.84 (m, 2H), 3.29 (br s, 1H), 2.96 (br s, 1H), 2.25 (dd, *J* = 6.7, 6.7 Hz, 2H), 2.07 (s, 3H), 1.88–1.65 (m, 2H), 1.65–1.39 (m, 3H), 0.92 (d, *J* = 7.2 Hz, 6H).

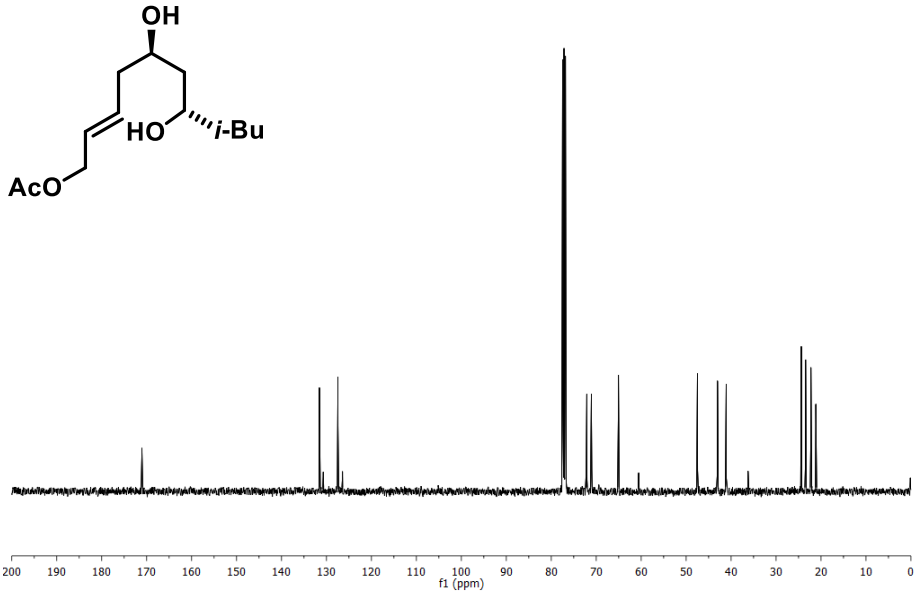
^{13}C NMR (100 MHz, $CDCl_3$, mixture of *E*- and *Z* isomers) δ 171.0, 131.6, 130.7, 127.5, 126.4, 72.3, 72.1, 71.1, 71.0, 65.1, 60.6, 47.5, 43.2, 43.0, 41.1, 36.2, 24.4, 23.4, 22.3, 21.1.

IR (neat) 3378, 2953, 2869, 1738, 1224, 969 cm^{-1}.

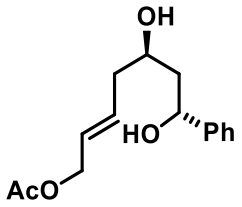
LRMS (ESI+) calcd. for $C_{13}H_{24}O_4Na$ $[M+Na]^+$ 267, found 267.

$[\alpha]^{25}_D$ = –20.02 ° (c = 0.60, $CHCl_3$).


OH
HO
i-Bu
AcO
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
i-Bu
AcO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(5*R*,7*R*,*E*)-5,7-Dihydroxy-7-phenylhept-2-en-1-yl Acetate (*syn*-2.3c).



According to general procedure for cross metathesis with ***syn*-2.2c** (50 mg, 0.26 mmol, 100 mol%), the product ***syn*-2.3c** was obtained as a brown oil in 80% yield (55.5 mg, 0.21 mmol, *E*:*Z* = 14:1) after flash column chromatography (hexanes/EtOAc = 3:1 to 2:1).

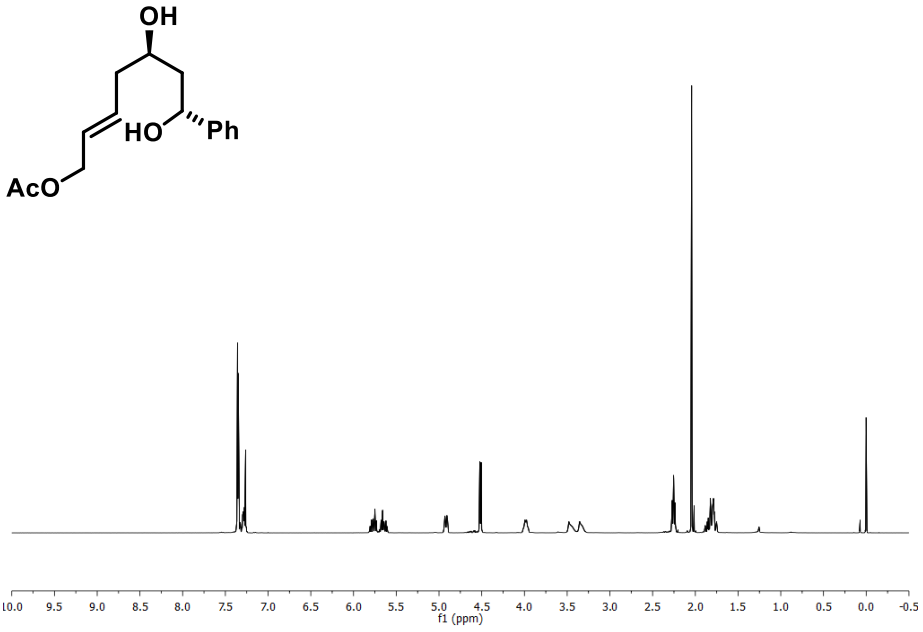
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5H), 5.85–5.56 (m, 2H), 4.92 (d, *J* = 9.5 Hz, 1H), 4.52 (d, *J* = 6.1 Hz, 2H), 3.98 (d, *J* = 7.1 Hz, 1H), 3.48 (br s, 1H), 3.35 (br s, 1H), 2.25 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.04 (s, 3H), 1.91–1.70 (m, 2H).

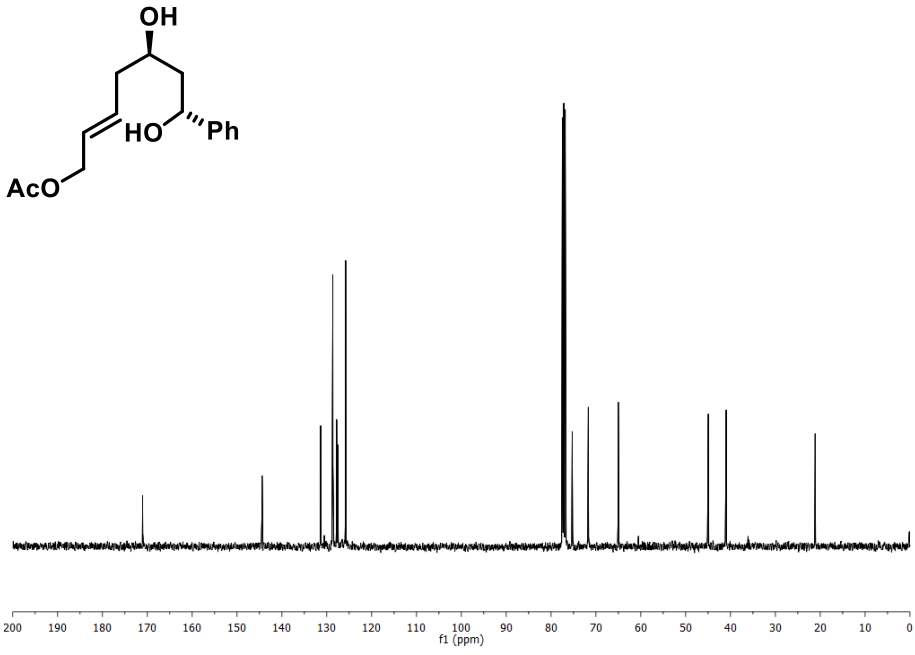
^{13}C NMR (100 MHz, $CDCl_3$, mixture of *E*- and *Z* isomers) δ 171.1, 144.4, 131.4, 128.7, 127.8, 127.6, 125.8, 75.3, 71.7, 65.0, 44.9, 41.0, 21.1.

IR (neat) 3365, 2916, 1735, 1230, 1025, 971 cm^{-1}.

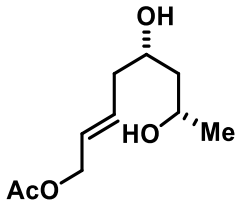
LRMS (ESI+) calcd. for $C_{15}H_{20}O_4Na$ $[M+Na]^+$ 287, found 287.

$[\alpha]^{25}_D$ = +22.05 ° (c = 1.40, $CHCl_3$).


OH
HO
Ph
AcO
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
Ph
AcO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(5*S*,7*S*,*E*)-5,7-Dihydroxyoct-2-en-1-yl Acetate (*anti*-2.3a).



According to general procedure for cross metathesis with ***anti*-2.2a** (100 mg, 0.77 mmol, 100 mol%), the product ***anti*-2.3a** was obtained as a brown oil in 82% yield (128 mg, 0.63 mmol, *E*:*Z* = 5:1) after flash column chromatography (hexanes/EtOAc = 2:1 to 1:1).

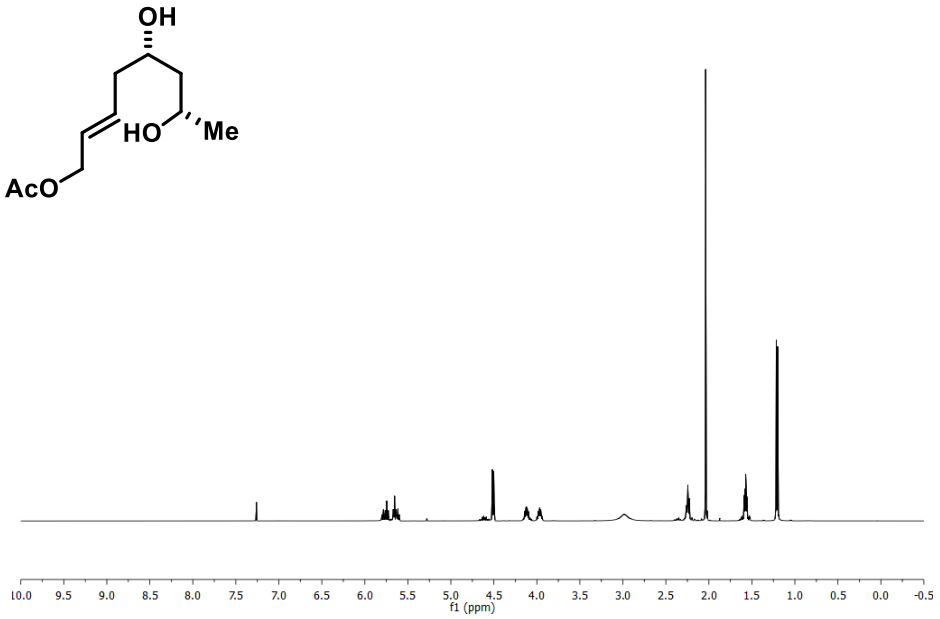
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82–5.58 (m, 2H), 4.51 (dd, *J* = 6.2, 0.9 Hz, 2H), 4.17–4.05 (m, 1H), 4.01–3.91 (m, 1H), 2.98 (br s, 2H), 2.29–2.21 (m, 2H), 2.04 (s, 3H), 1.67–1.49 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H).

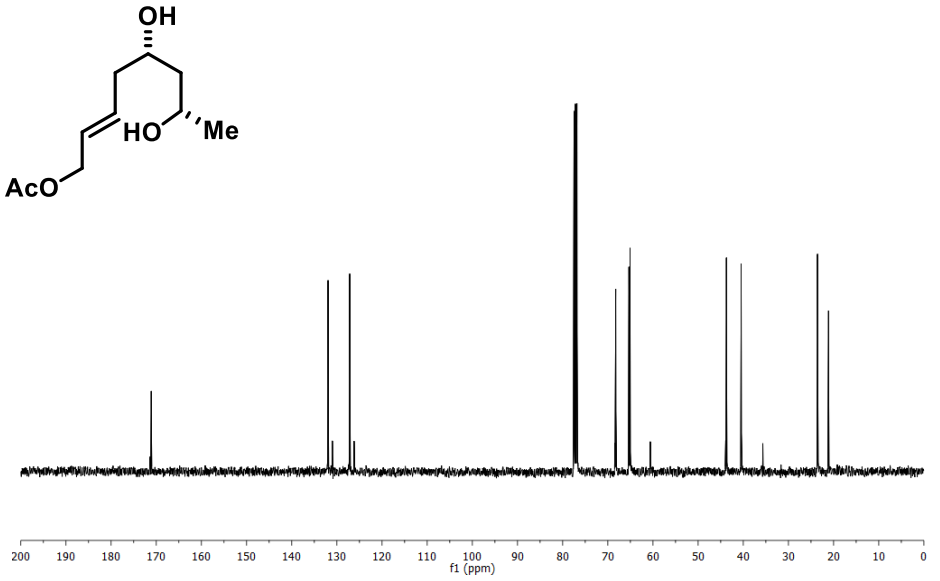
^{13}C NMR (100 MHz, $CDCl_3$, mixture of *E*- and *Z* isomer) δ 171.3, 171.1, 132.0, 131.0, 127.2, 126.2, 68.4, 68.2, 65.3, 65.1, 60.6, 43.9, 43.7, 40.5, 35.7, 23.6, 21.1.

IR (neat) 3382, 2934, 1736, 1230, 1024 cm^{-1}.

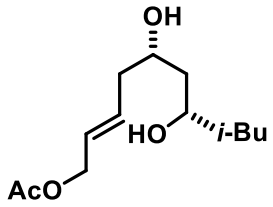
HRMS (ESI+) calcd. for $C_{10}H_{18}O_4Na$ $[M+Na]^+$ 225.1097, found 225.1099.

$[\alpha]^{25}_D$ = +16.67 ° (c = 0.58, $CHCl_3$).


OH
HO
Me
AcO
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
Me
AcO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(5*S*,7*S*,*E*)-5,7-Dihydroxy-9-methyldec-2-en-1-yl Acetate (*anti*-2.3b).



According to general procedure for cross metathesis with ***anti*-2.2b** (100 mg, 0.58 mmol, 100 mol%), the product ***anti*-2.3b** was obtained as a brown oil in 81% yield (114 mg, 0.47 mmol, *E*:*Z* = 2:1) after flash column chromatography (hexanes/EtOAc = 3:1 to 2:1).

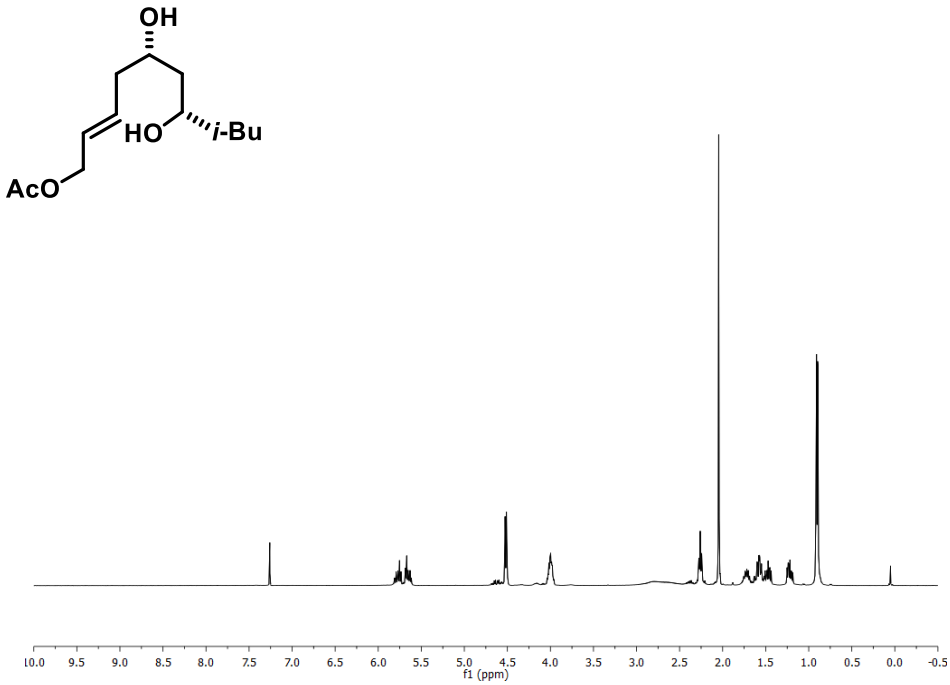
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85–5.57 (m, 2H), 4.52 (d, *J* = 6.1 Hz, 2H), 4.07–3.93 (m, 2H), 2.80 (br s, 2H), 2.26 (dd, *J* = 6.5, 6.5 Hz, 2H), 2.05 (s, 3H), 1.82–1.66 (m, 1H), 1.66–1.42 (m, 2H), 1.27–1.16 (m, 1H), 0.91 (d, *J* = 2.0 Hz, 3H), 0.90 (d, *J* = 1.9 Hz, 3H), 0.92–0.86 (m, 1H).

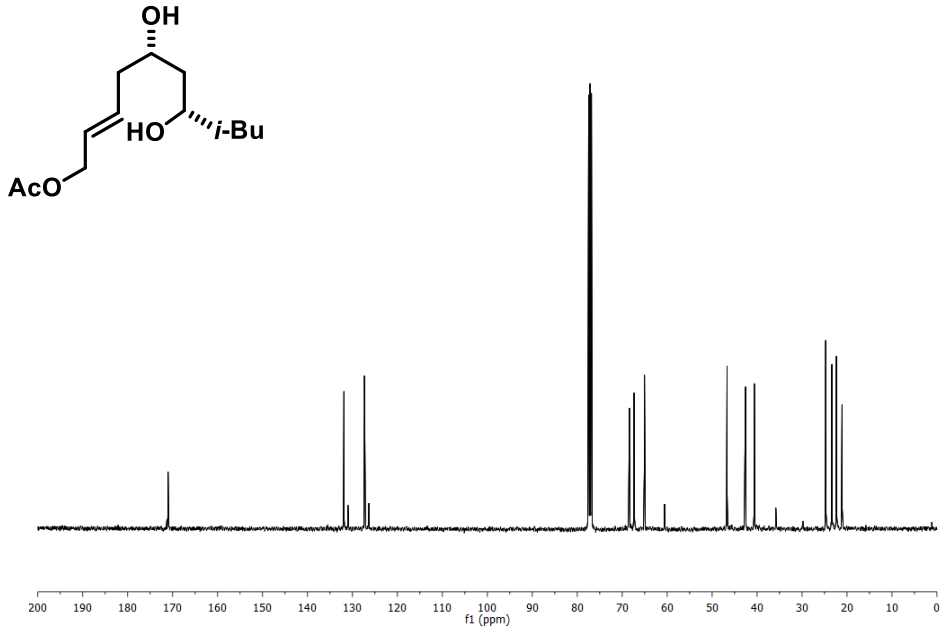
^{13}C NMR (100 MHz, $CDCl_3$, mixture of *E*- and *Z* isomers) δ 171.3, 171.0, 131.9, 131.0, 127.3, 126.3, 68.6, 68.4, 67.4, 65.0, 60.6, 46.7, 42.8, 42.6, 40.6, 35.8, 24.7, 23.4, 22.4, 21.1.

IR (neat) 3406, 2953, 1736, 1229, 1024, 969 cm^{-1}.

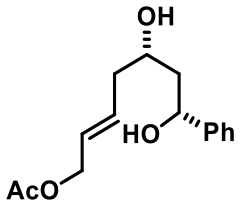
LRMS (ESI+) calcd. for $C_{13}H_{24}O_4Na$ $[M+Na]^+$ 267, found 267.

$[\alpha]^{25}_D$ = –18.87 ° (c = 0.53, $CHCl_3$).


OH
HO
i-Bu
AcO
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
i-Bu
AcO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(5*S*,7*R*,*E*)-5,7-Dihydroxy-7-phenylhept-2-en-1-yl Acetate (*anti*-2.3c).



According to general procedure for cross metathesis with ***anti*-2.2c** (28 mg, 0.15 mmol, 100 mol%), the product ***anti*-2.3c** was obtained as a brown oil in 78% yield (31 mg, 0.12 mmol, *E*:*Z* = 7:1) after flash column chromatography (hexanes/EtOAc = 3:1 to 2:1).

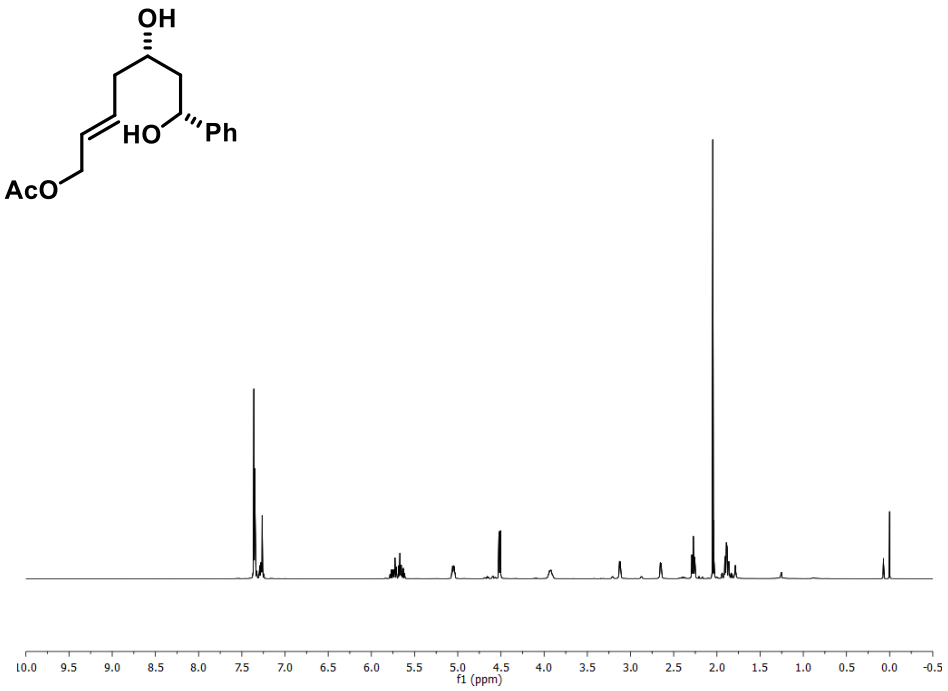
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.22 (m, 5H), 5.82–5.54 (m, 2H), 5.09–5.01 (m, 1H), 4.51 (dd, *J* = 6.0, 0.7 Hz, 2H), 3.98–3.88 (m, 1H), 3.12 (d, *J* = 4.0 Hz, 1H), 2.65 (d, *J* = 3.8 Hz, 1H), 2.27 (dd, *J* = 6.8, 6.8 Hz, 2H), 2.05 (s, 3H), 1.96–1.81 (m, 2H).

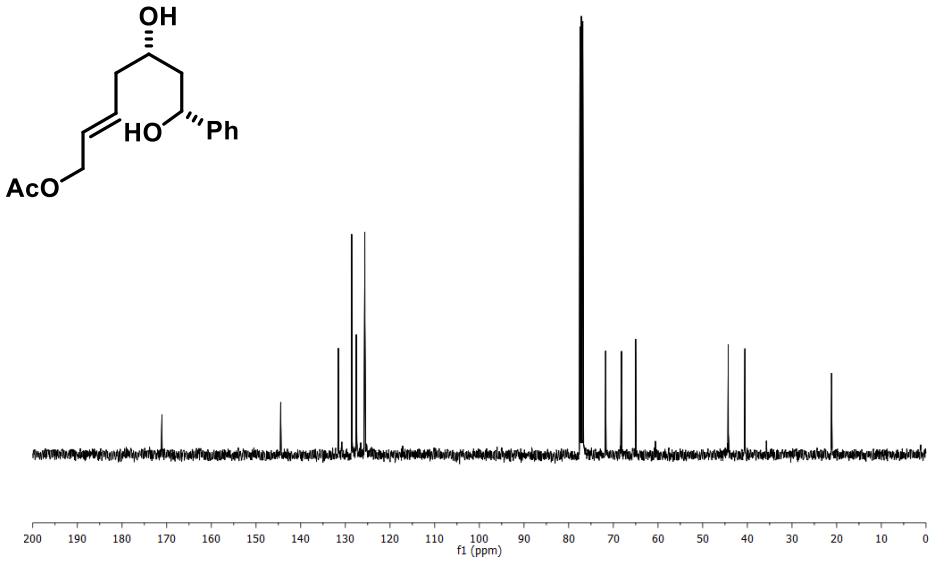
^{13}C NMR (100 MHz, $CDCl_3$, mixture of *E*- and *Z* isomers) δ 171.1, 144.5, 131.6, 128.6, 127.6, 127.5, 125.6, 71.7, 68.2, 65.0, 44.3, 40.5, 21.1.

IR (neat) 3392, 2916, 1734, 1233, 1026, 969 cm^{-1}.

LRMS (ESI+) calcd. for $C_{15}H_{20}O_4Na$ $[M+Na]^+$ 287, found 287.

$[\alpha]^{25}_D$ = –56.41 ° (c = 0.26, $CHCl_3$).


OH
HO
Ph
AcO
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
HO
Ph
AcO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

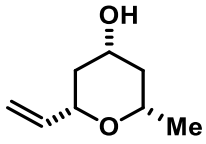
General Procedure for Pd-Catalyzed *O*-Allylation.

To a round bottomed flask under an argon atmosphere charged with $Pd_2(dba)_3$-$CHCl_3$ and DPPBA was added freshly distilled CH_2Cl_2 (0.006 M to Pd catalyst). The mixture was allowed to stir at ambient temperature for 30 minutes, during which time the color of the solution changed from purple to orange. The orange solution was transferred *via* syringe to a round-bottomed flask charged with a solution of acetate **2.3** (100 mol%) and Et_3N (200 mol%) in CH_2Cl_2 (0.013 M). The reaction mixture was allowed to stir at indicated temperature for indicated time. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography to furnish the title.

General Procedure for Ir-Catalyzed *O*-Allylation.

To a sealed tube under an argon atmosphere charged with $[Ir(cod)Cl]_2$ (3 mol%) and (*S*,*S*,*aS*)-L (6 mol%) was added TBD (50 mol%) in THF (0.33 M to Ir catalyst). The reaction mixture was allowed to stir at ambient temperature for 10 min, at which point a solution of acetate **2.3** (100 mol%) in THF (0.3 M) was added *via* syringe. The reaction mixture was placed in a 90 °C oil bath and was allowed to stir for 20 h. The reaction mixture was allowed to cool to ambient temperature, and was concentrated *in vacuo*. The residue was subjected to flash column chromatography to furnish the title and unreacted acetate **2.3.**

(2*S*,4*R*,6*S*)-2-Methyl-6-vinyltetrahydro-2H-pyran-4-ol (2,6-*cis*-2.4a).



According to general procedure for Pd-catalyzed *O*-allylation with ***anti*-2.3a** (40.4 mg, 0.20 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (6.2 mg, 0.006 mmol, 3 mol%), and (*S*,*S*)-DPPBA (12.4 mg, 0.018 mmol, 9 mol%) at 25 °C for 3 h, the product **2,6-*cis*-2.4a** was obtained as a colorless oil in 99% yield (28.2 mg, 0.198 mmol, *dr* = >20:1) after flash column chromatography (hexanes/EtOAc = 3:2 to 2:3).

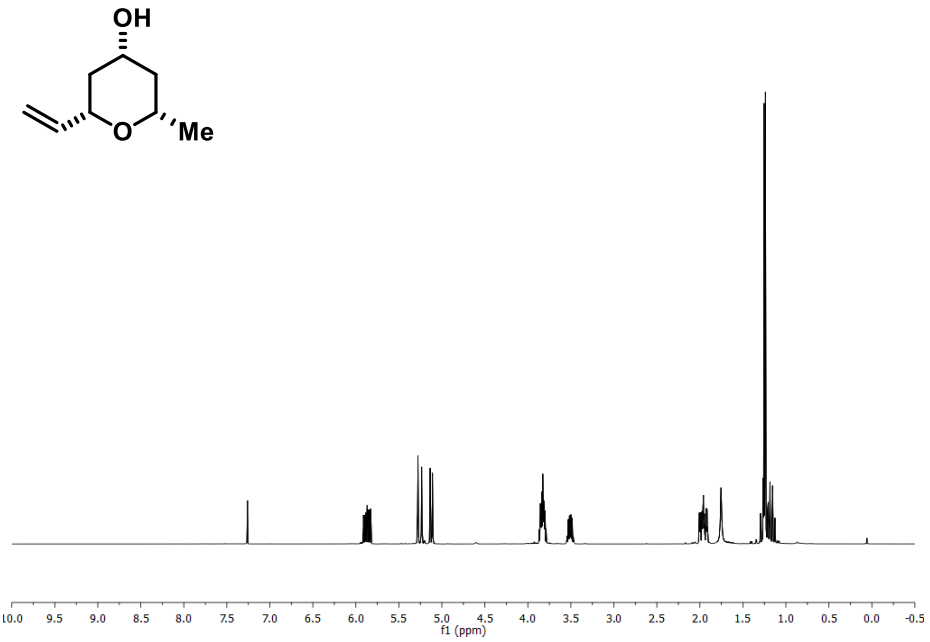
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.26 (ddd, *J* = 17.3, 1.4, 1.4 Hz, 1H), 5.12 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 3.88–3.77 (m, 2H), 3.56–3.45 (m, 1H), 2.02–1.90 (m, 2H), 1.75 (br s, 1H), 1.30–1.12 (m, 2H), 1.25 (d, *J* = 6.2 Hz, 3H).

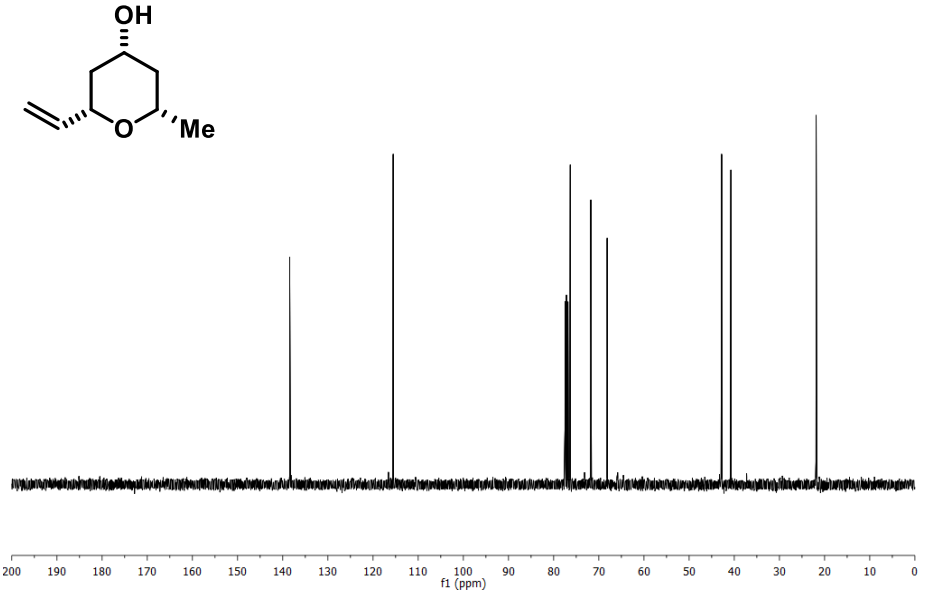
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 115.5, 76.3, 71.8, 68.1, 42.8, 40.7, 21.9.

IR (neat) 3357, 2973, 2847, 1368, 1308, 1146, 1014, 922 cm^{-1}.

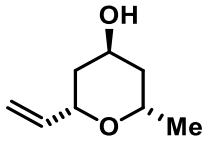
HRMS (ESI+) calcd. for $C_8H_{14}O_2Na$ $[M+Na]^+$ 165.0886, found 165.0886.

$[\alpha]^{25}_D$ = –18.10 ° (c = 1.05, $CHCl_3$).


OH
O
Me
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*S*,4*S*,6*S*)-2-Methyl-6-vinyltetrahydro-2H-pyran-4-ol (4-*epi*-2,6-*cis*-2.4a).



According to general procedure for Pd-catalyzed *O*-allylation with ***syn*-2.3a** (20.2 mg, 0.10 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (3.1 mg, 0.003 mmol, 3 mol%), and (*S*,*S*)-DPPBA (6.2 mg, 0.009 mmol, 9 mol%) at 50 °C for 18 h, the product **4-*epi*-2,6-*cis*-2.4a** was obtained as a colorless oil in 90% yield (12.8 mg, 0.090 mmol, *dr* = >20:1) after flash column chromatography (hexanes/EtOAc = 3:2).

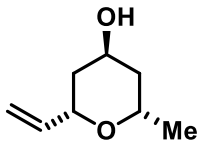
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 17.3, 10.6, 5.9 Hz, 1H), 5.27 (ddd, *J* = 17.3, 1.5, 1.5 Hz, 1H), 5.12 (ddd, *J* = 10.6, 1.3, 1.3 Hz, 1H), 4.35–4.24 (m, 2H), 4.03–3.92 (m, 1H), 1.75–1.36 (m, 5H), 1.20 (d, *J* = 6.2 Hz, 3H).

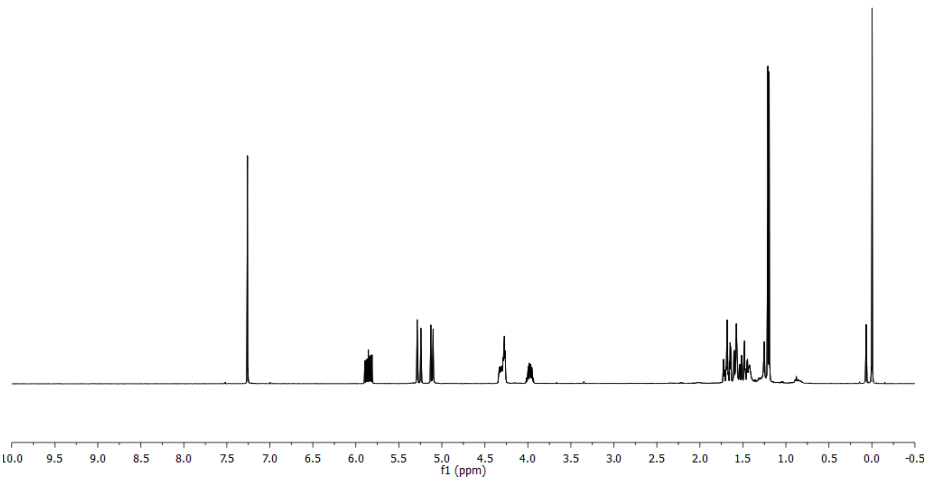
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 115.3, 72.5, 67.7, 64.8, 40.2, 38.3, 22.0.

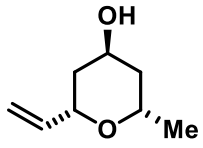
IR (neat) 3357, 2920, 2851, 1632, 1365, 1259, 1018, 965 cm^{-1}.

LRMS (CI+) calcd. for $C_8H_{15}O_2$ $[M+H]^+$ 143, found 143.

$[\alpha]^{25}_D$ = –11.11 ° (c = 0.09, $CHCl_3$).

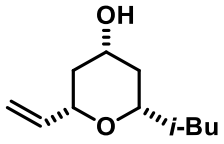

OH
O
Me


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
Me

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*S*,4*R*,6*S*)-2-Isobutyl-6-vinyltetrahydro-2H-pyran-4-ol (2,6-*cis*-2.4b).



According to general procedure for Pd-catalyzed *O*-allylation with ***anti*-2.3b** (24.4 mg, 0.10 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (3.1 mg, 0.003 mmol, 3 mol%), and (*S*,*S*)-DPPBA (6.2 mg, 0.009 mmol, 9 mol%) at 50 °C for 20 h, the product **2,6-*cis*-2.4b** was obtained as a colorless oil in 84% yield (15.4 mg, 0.084 mmol, *dr* = >20:1) after flash column chromatography (hexanes/EtOAc = 2:1).

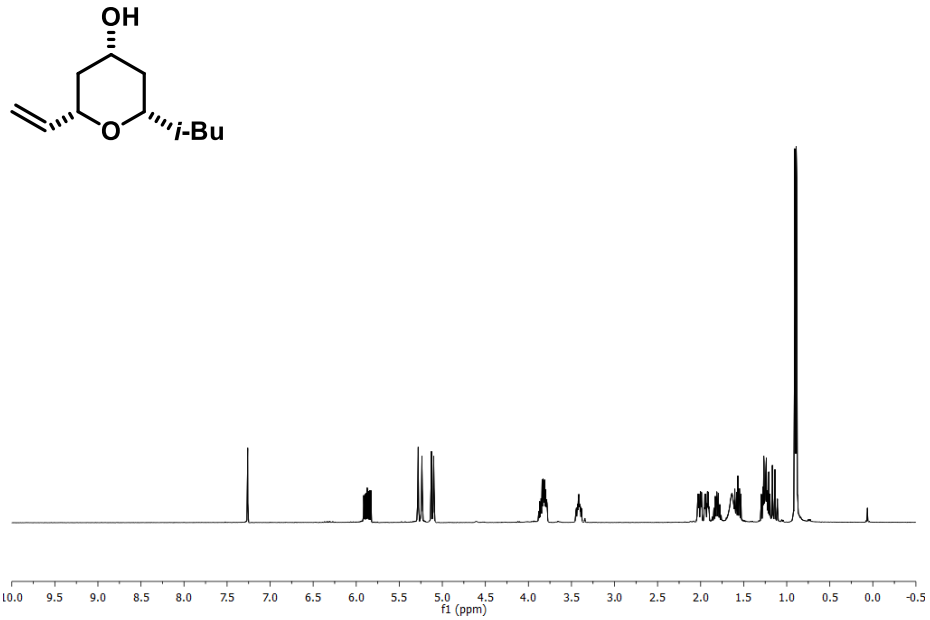
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 17.3, 10.6, 5.3 Hz, 1H), 5.26 (ddd, *J* = 17.3, 1.5, 1.5 Hz, 1H), 5.11 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1H), 3.90–3.77 (m, 2H), 3.47–3.37 (m, 1H), 2.05–1.97 (m, 1H), 1.97–1.89 (m, 1H), 1.88–1.74 (m, 1H), 1.64 (br s, 1H), 1.61–1.51 (m, 1H), 1.32–1.09 (m, 3H), 0.90 (d, *J* =2.3 Hz, 3H), 0.89 (d, *J* = 2.2 Hz, 3H).

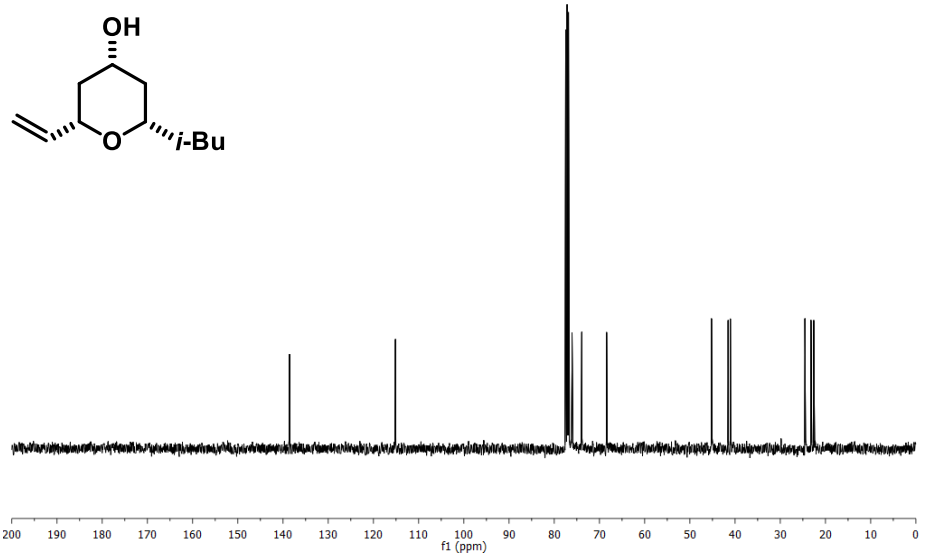
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 115.1, 76.1, 73.9, 68.4, 45.2, 41.5, 41.0, 24.5, 23.2, 22.6.

IR (neat) 3357, 2954, 1383, 1036 cm^{-1}.

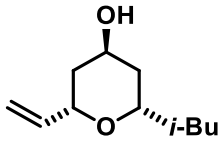
LRMS (CI+) calcd. for $C_{11}H_{21}O_2$ $[M+H]^+$ 185, found 185.

$[\alpha]^{25}_D$ = –49.49 ° (c = 0.99, $CHCl_3$).


OH
O
i-Bu
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
i-Bu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*S*,4*S*,6*S*)-2-Isobutyl-6-vinyltetrahydro-2H-pyran-4-ol (4-*epi*-2,6-*cis*-2.4b).



According to general procedure for Pd-catalyzed *O*-allylation with ***syn*-2.3b** (24.4 mg, 0.10 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (5.2 mg, 0.005 mmol, 5 mol%), and (*S*,*S*)-DPPBA (10.4 mg, 0.015 mmol, 15 mol%) at 25 °C for 18 h, the product **4-*epi*-2,6-*cis*-2.4b** was obtained as a colorless oil in 75% yield (13.8 mg, 0.075 mmol, *dr* = >20:1) after flash column chromatography (hexanes/EtOAc = 3:2 to1:1).

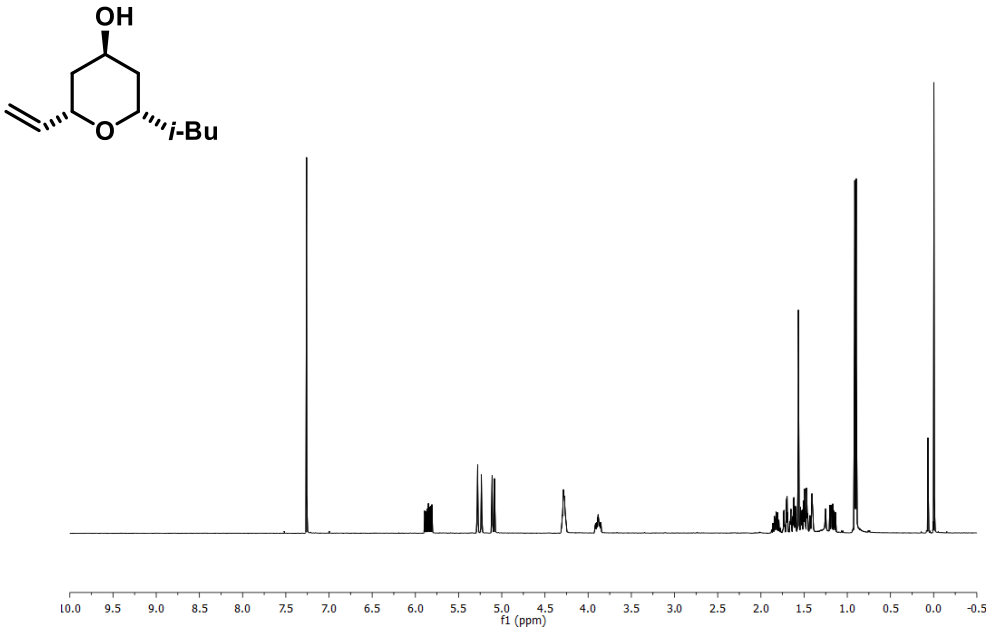
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 17.3, 10.6, 5.3 Hz, 1H), 5.26 (ddd, *J* = 17.3, 1.6, 1.6 Hz, 1H), 5.10 (ddd, *J* = 10.6, 1.5, 1.5 Hz, 1H), 4.33–4.24 (m, 2H), 3.93–3.84 (m, 1H), 1.90–1.39 (m, 7H), 1.17 (ddd, *J* = 13.7, 8.1, 4.7 Hz, 1H), 0.92 (d, *J* = 0.8 Hz, 3H) 0.90 (d, *J* = 0.7 Hz, 3H).

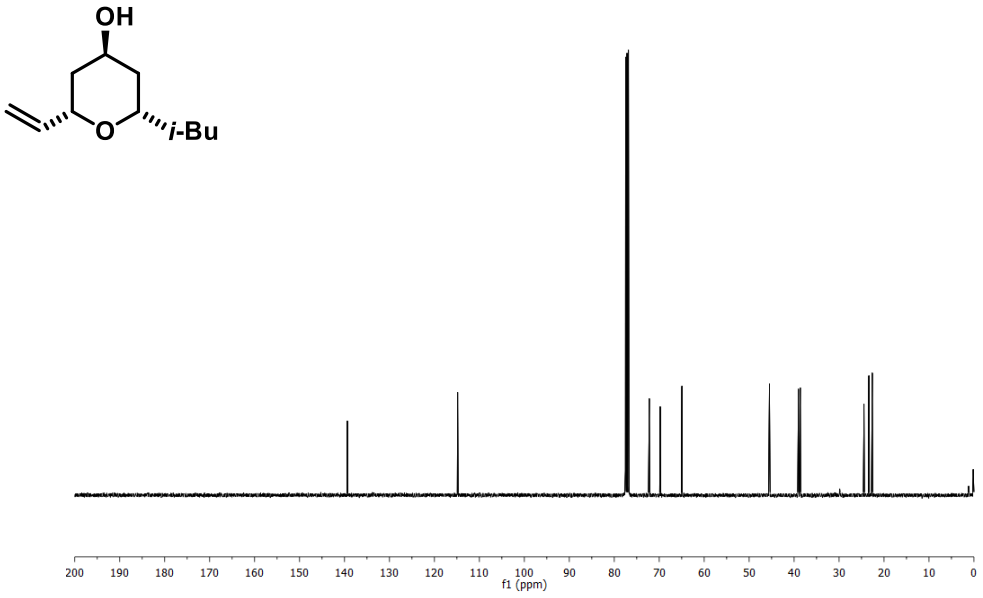
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 114.8, 72.2, 69.8, 64.9, 45.5, 39.0, 38.6, 24.5, 23.4, 22.6.

IR (neat) 3394, 2953, 2869, 1376, 1260, 1095, 1037, 920 cm^{-1}.

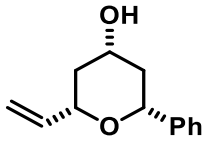
LRMS (ESI+) calcd. for $C_{11}H_{20}O_2Na$ $[M+Na]^+$ 207, found 207.

$[\alpha]^{25}_D$ = –12.82 ° (c = 0.26, $CHCl_3$).


OH
O
i-Bu
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
i-Bu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*R*,4*S*,6*S*)-2-Phenyl-6-vinyltetrahydro-2H-pyran-4-ol (2,6-*cis*-2.4c).



According to general procedure for Pd-catalyzed *O*-allylation with ***anti*-2.3c** (26.4 mg, 0.10 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (3.1 mg, 0.003 mmol, 3 mol%), and (*S*,*S*)-DPPBA (6.2 mg, 0.009 mmol, 9 mol%) at 50 °C for 22 h, the product **2,6-*cis*-2.4c** was obtained as a colorless oil in 89% yield (18.2 mg, 0.089 mmol, *dr* = >20:1) after flash column chromatography (hexanes/EtOAc = 2:1).

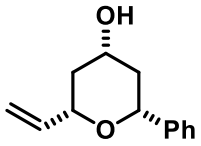
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.23 (m, 5H), 5.96 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.33 (ddd, *J* = 17.3, 1.5, 1.5 Hz, 1H), 5.16 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1H), 4.44 (dd, *J* = 11.4, 2.0 Hz, 1H), 4.08–3.96 (m, 2H), 2.24–2.17 (m, 1H), 2.15–2.07 (m, 1H), 1.69 (br, 1H), 1.57–1.33 (m, 2H).

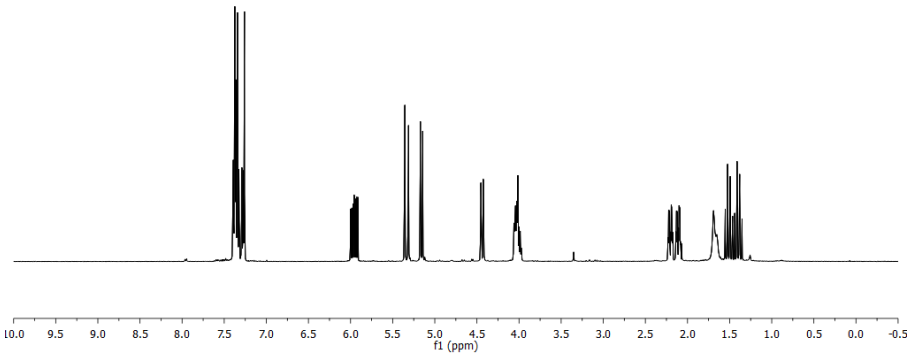
^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 138.3, 128.5, 127.7, 126.1, 115.3, 77.7, 76.6, 68.5, 43.1, 40.9.

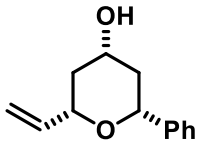
IR (neat) 3358, 2944, 2850, 1059, 698 cm^{-1}.

LRMS (CI+) calcd. for $C_{11}H_{17}O_2$ $[M+H]^+$ 205, found 205.

$[\alpha]^{25}_D$ = +52.17 ° (c = 0.46, $CHCl_3$).

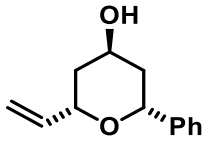

OH
O
Ph


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
Ph

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*R*,4*R*,6*S*)-2-Phenyl-6-vinyltetrahydro-2H-pyran-4-ol (4-*epi*-2,6-*cis*-2.4c).



According to general procedure for Pd-catalyzed *O*-allylation with ***syn*-2.3c** (26.4 mg, 0.10 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (5.2 mg, 0.005 mmol, 5 mol%), and (*S*,*S*)-DPPBA (10.4 mg, 0.015 mmol, 15 mol%) at 25 °C for 18 h, the product **2,6-*cis*-2.4c** was obtained as a colorless oil in 96% yield (19.6 mg, 0.096 mmol, *dr* = >20:1) after flash column chromatography (hexanes/EtOAc = 3:2 to1:1).

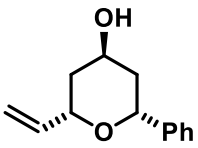
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.13 (m, 5H), 5.93 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1H), 5.33 (ddd, *J* = 17.3, 1.6, 1.6 Hz, 1H), 5.13 (ddd, *J* = 10.6, 1.5, 1.5 Hz, 1H), 4.92 (dd, *J* = 11.7, 2.4 Hz, 1H), 4.57–4.45 (m, 1H), 4.40–4.32 (m, 1H), 1.94–1.86 (m, 1H), 1.84–1.62 (m, 4H).

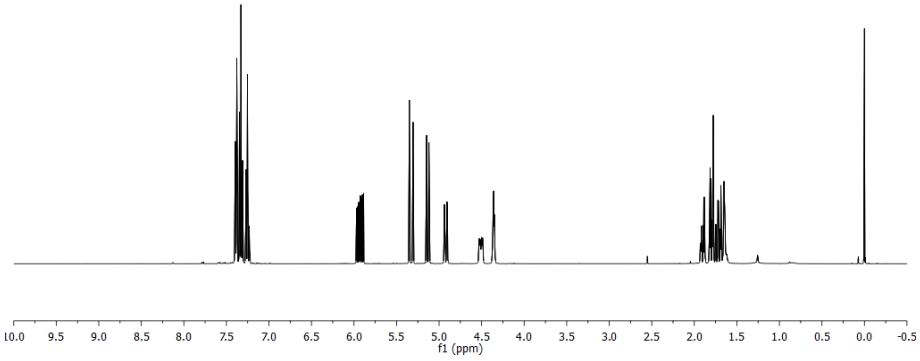
^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 139.1, 128.4, 127.4, 126.1, 115.1, 73.7, 72.8, 64.9, 40.7, 38.4.

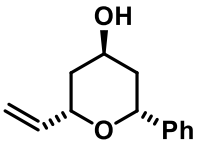
IR (neat) 3400, 2919, 2824, 1453, 1304, 1179, 1023, 920 cm^{-1}.

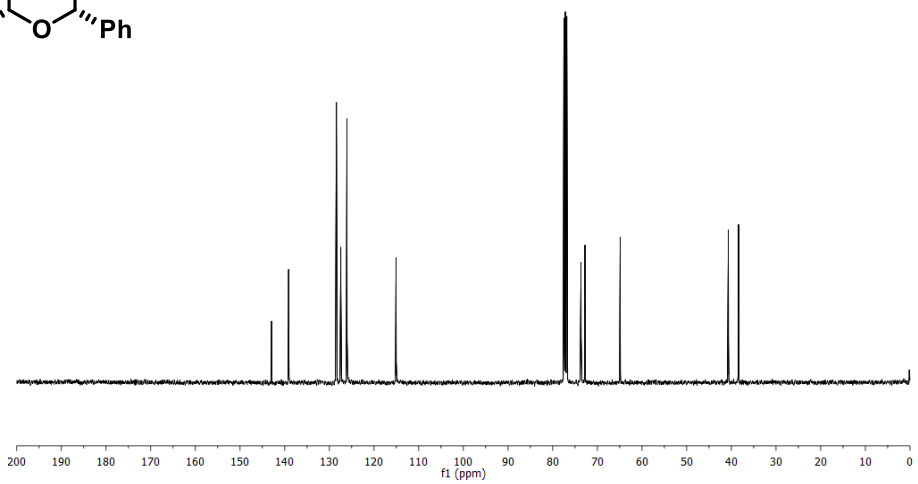
LRMS (ESI+) calcd. for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227, found 227.

$[\alpha]^{25}_D$ = +38.65 ° (c = 0.12, $CHCl_3$).

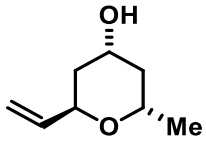

OH
O
Ph


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
Ph


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*S*,4*R*,6*R*)-2-Methyl-6-vinyltetrahydro-2H-pyran-4-ol (2,6-*trans*-2.4a).



According to general procedure for Pd-catalyzed *O*-allylation with ***anti*-2.3a** (40.4 mg, 0.20 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (6.2 mg, 0.006 mmol, 3 mol%), and (*R*,*R*)-DPPBA (12.4 mg, 0.018 mmol, 9 mol%) at 25 °C for 3 h, the product **2,6-*trans*-2.4a** was obtained as a colorless oil in 99% yield (28.1 mg, 0.198 mmol, *dr* = 1:4, **2,6-*cis*-2.4a**:**2,6-*trans*-2.4a**) after flash column chromatography (hexanes/EtOAc = 3:2 to 2:3).

According to general procedure for Ir-catalyzed *O*-allylation with ***anti*-2.3a** (20.2 mg, 0.10 mmol, 100 mol%), the product **2,6-*trans*-2.4a** was obtained as a colorless oil in 61% yield (8.7 mg, 0.061 mmol, *dr* = 1:8, **2,6-*cis*-2.4a**:**2,6-*trans*-2.4a**) after flash column chromatography (hexanes/EtOAc = 3:2 to 2:3). The unreacted ***anti*-2.3a** was recovered in 21% (4.3 mg, 0.021 mmol). Yield based on recovered starting material (BRSM) was 74%.

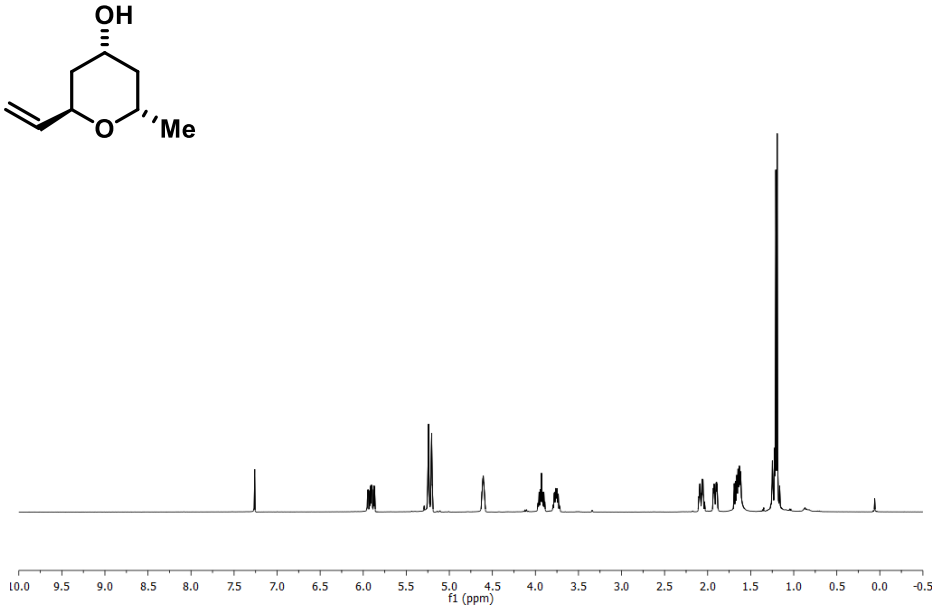
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 17.9, 10.6, 4.1 Hz, 1H), 5.26–5.22 (m, 1H), 5.22–5.17 (m, 1H), 4.65–4.54 (m, 1H), 3.93 (ddd, *J* = 15.4, 10.9, 4.5 Hz, 1H), 3.80–3.67 (m, 1H), 2.12–2.00 (m, 1H), 1.96–1.87 (m, 1H), 1.75–1.53 (m, 2H), 1.27–1.16 (m, 1H), 1.20 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 116.6, 73.2, 65.8, 64.5, 43.3, 37.3, 21.9.

IR (neat) 3356, 2932, 1370, 1122, 1039, 919 cm^{-1}.

HRMS (ESI+) calcd. for $C_8H_{14}O_2Na$ $[M+Na]^+$ 165.0886, found 165.0887.

$[\alpha]^{25}_D$ = –64.18 ° (c = 0.67, $CHCl_3$).


OH
O
Me
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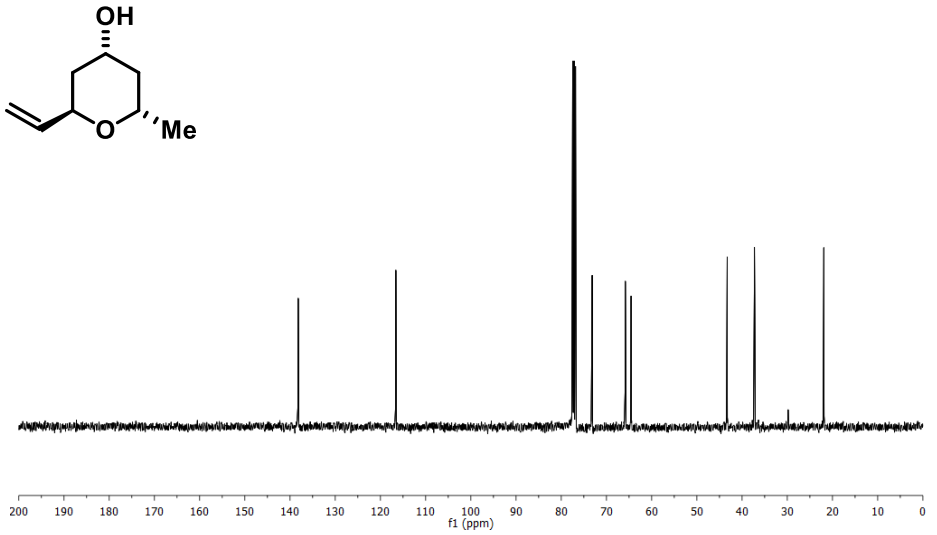
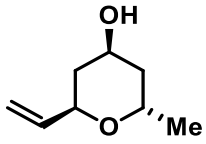
f1 (ppm)


OH
O
Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*S*,4*S*,6*R*)-2-Methyl-6-vinyltetrahydro-2H-pyran-4-ol (4-*epi*-2,6-*trans*-2.4a).



According to general procedure for Pd-catalyzed *O*-allylation with ***anti*-2.3a** (20.2 mg, 0.10 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (5.2 mg, 0.005 mmol, 5 mol%), and (*R*,*R*)-DPPBA (10.4 mg, 0.015 mmol, 15 mol%) at 25 °C for 18 h, the product **4-*epi*-2,6-*trans*-2.4a** was obtained as a colorless oil in 90% yield (12.8 mg, 0.090 mmol, *dr* = 1:2, **4-*epi*-2,6-*cis*-2.4a**:**4-*epi*-2,6-*trans*-2.4a**) after flash column chromatography (hexanes/EtOAc = 3:2 to 2:3).

According to general procedure for Ir-catalyzed *O*-allylation with ***syn*-2.3a** (20.2 mg, 0.10 mmol, 100 mol%), the product **4-*epi*-2,6-*trans*-2.4a** was obtained as a colorless oil in 55% yield (7.8 mg, 0.055 mmol, dr = 1:3, **4-*epi*-2,6-*cis*-2.4a**:**4-*epi*-2,6-*trans*-2.4a**) after flash column chromatography (hexanes/EtOAc = 3:2 to 2:3). The unreacted ***syn*-2.3a** was recovered in 26% (5.2 mg, 0.026 mmol). Yield based on recovered starting material (BRSM) was 69%.

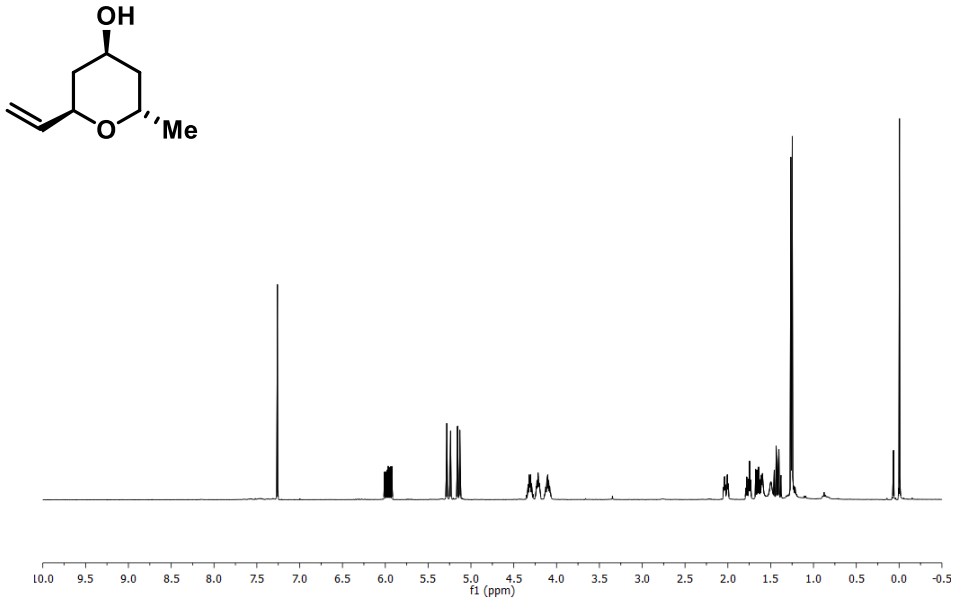
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 17.4, 10.6, 5.5 Hz, 1H), 5.26 (ddd, *J* = 17.4, 1.5, 1.5 Hz, 1H), 5.14 (ddd, *J* = 10.6, 1.5, 1.5 Hz, 1H), 4.36–4.26 (m, 1H), 4.26–4.18 (m, 1H), 4.15–4.04 (m, 1H), 2.06–1.97 (m, 1H), 1.80–1.72 (m, 1H), 1.69–1.58 (m, 1H), 1.50 (br s, 1H), 1.47–1.37 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 3H).

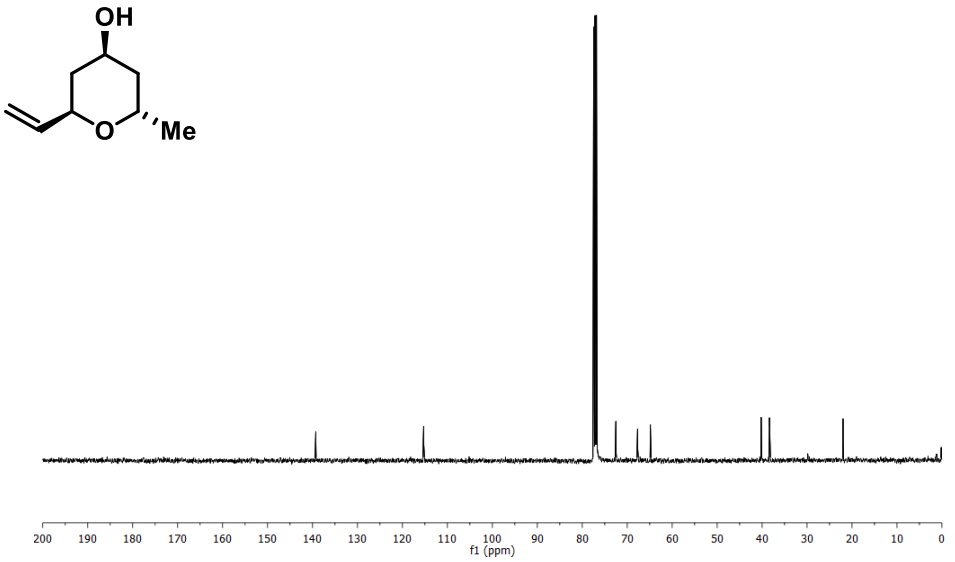
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 115.3, 70.0, 67.2, 64.5, 40.1, 39.4, 19.0.

IR (neat) 3354, 2928, 1645, 1376, 1186, 1020, 921 cm^{-1}.

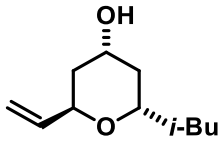
LRMS (CI+) calcd. for $C_8H_{15}O_2$ $[M+H]^+$ 143, found 143.

$[\alpha]^{25}_D$ = –38.89 ° (c = 0.18, $CHCl_3$).


OH
O
Me
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*S*,4*R*,6*R*)-2-Isobutyl-6-vinyltetrahydro-2H-pyran-4-ol (2,6-*trans*-2.4b).



According to general procedure for Pd-catalyzed *O*-allylation with ***anti*-2.3b** (24.4 mg, 0.10 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (5.2 mg, 0.005 mmol, 5 mol%), and (*R*,*R*)-DPPBA (10.4 mg, 0.015 mmol, 15 mol%) at 25 °C for 20 h, the product **2,6-*trans*-2.4b** was obtained as a colorless oil in 73% yield (13.4 mg, 0.073 mmol, *dr* = 1:4, **2,6-*cis*-2.4b**:**2,6-*trans*-2.4b**) after flash column chromatography (hexanes/EtOAc = 3:2 to1:1).

According to general procedure for Ir-catalyzed *O*-allylation with ***anti*-2.3b** (24.4 mg, 0.10 mmol, 100 mol%), the product **2,6-*trans*-2.4b** was obtained as a colorless oil in 69% yield (12.7 mg, 0.069 mmol, *dr* = 1:9, **2,6-*cis*-2.4b**:**2,6-*trans*-2.4b**) after flash column chromatography (hexanes/EtOAc = 3:1 to 1:1). The unreacted ***anti*-2.3b** was recovered in 12% (3.0 mg, 0.012 mmol). Yield based on recovered starting material (BRSM) was 77%.

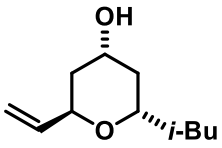
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98–5.83 (m, 1H), 5.27–5.24 (m, 1H), 5.22 (ddd, *J* = 3.8, 2.2, 1.3 Hz, 1H), 4.61 (ddd, *J* = 5.9, 3.9, 2.0 Hz, 1H), 4.01–3.88 (m, 1H), 3.72–3.60 (m, 1H), 2.17–2.05 (m, 1H), 1.96–1.84 (m, 1H), 1.86–1.74 (m, 1H), 1.73–1.62 (m, 1H), 1.54 (ddd, *J* = 14.1, 8.8, 5.5 Hz, 2H), 1.24–1.13 (m, 2H), 0.95–0.84 (t, *J* = 6.4 Hz, 6H).

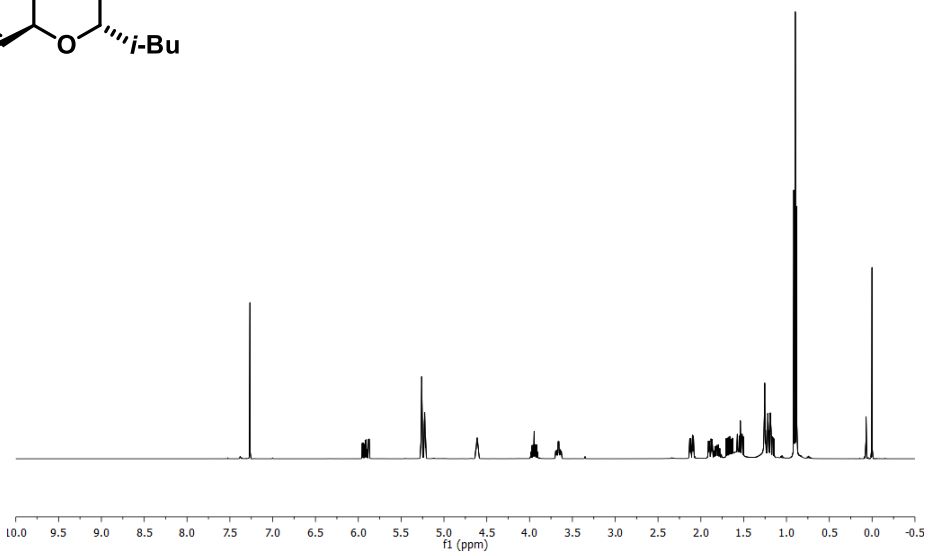
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 116.6, 72.9, 67.7, 64.7, 45.5, 42.2, 37.5, 24.4, 23.4, 22.2.

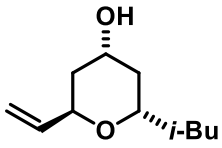
IR (neat) 3357, 2925, 2869, 1466, 1367, 1126, 1024, 986 cm^{-1}.

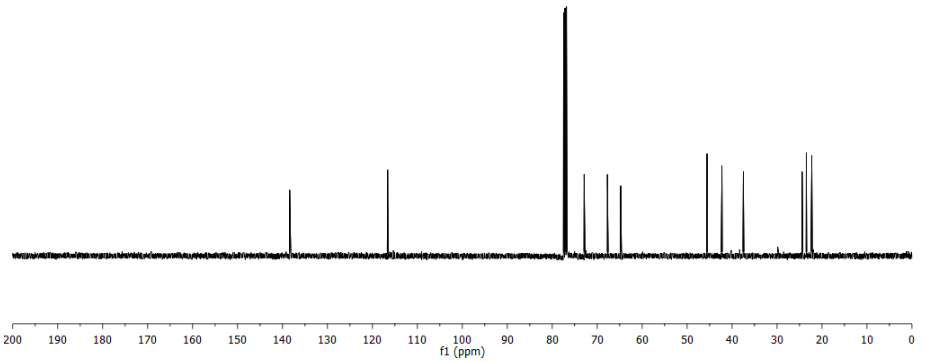
LRMS (ESI+) calcd. for $C_{11}H_{20}O_2Na$ $[M+Na]^+$ 207, found 207.

$[\alpha]^{25}_D$ = –74.07° (c = 0.27, $CHCl_3$).

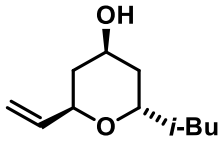

OH
O
i-Bu


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
i-Bu


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*S*,4*S*,6*R*)-2-Isobutyl-6-vinyltetrahydro-2H-pyran-4-ol (4-*epi*-2,6-*trans*-2.4b).



According to general procedure for Pd-catalyzed *O*-allylation with ***syn*-2.3b** (24.4 mg, 0.10 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (5.2 mg, 0.005 mmol, 5 mol%), and (*R*,*R*)-DPPBA (10.4 mg, 0.015 mmol, 15 mol%) at 25 °C for 18 h, the product **4-*epi*-2,6-*trans*-2.4b** was obtained as a colorless oil in 75% yield (14.2 mg, 0.077 mmol, *dr* = 1:1, **4-*epi*-2,6-*cis*-2.4b**:**4-*epi*-2,6-*trans*-2.4b**) after flash column chromatography (hexanes/EtOAc = 3:2 to1:1).

According to general procedure for Ir-catalyzed *O*-allylation with ***syn*-2.3b** (40.0 mg, 0.18 mmol, 100 mol%), the product **4-*epi*-2,6-*trans*-2.4b** was obtained as a colorless oil in 56% yield (18.7 mg, 0.10 mmol, dr = 1:6, **4-*epi*-2,6-*cis*-2.4b**:**4-*epi*-2,6-*trans*-2.4b**) after flash column chromatography (hexanes/EtOAc = 4:1 to 2:1). The unreacted ***syn*-2.3b** was recovered in 21% (9.2 mg, 0.038 mmol). Yield based on recovered starting material (BRSM) was 68%.

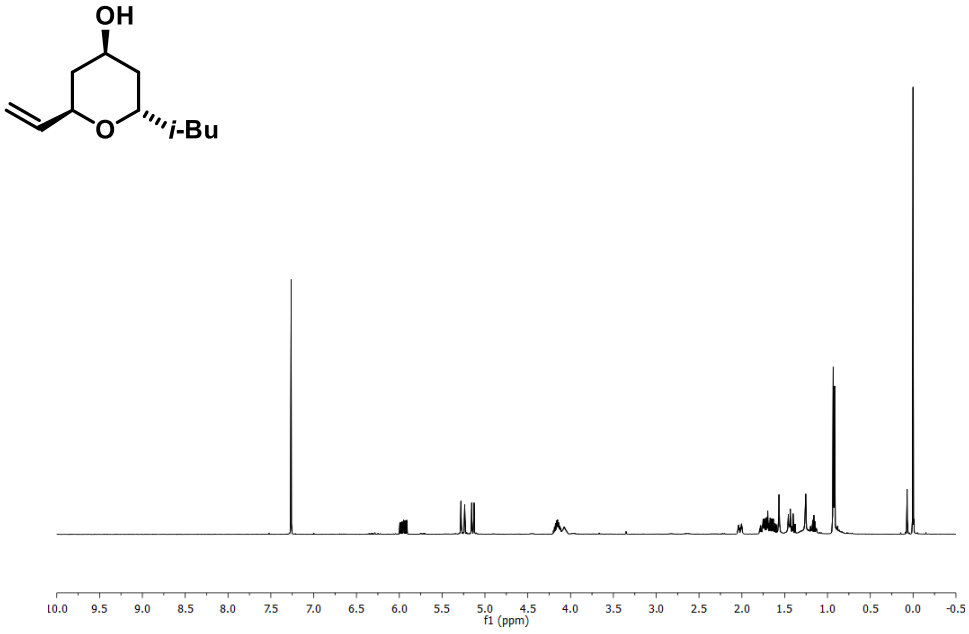
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.26 (ddd, *J* = 17.4, 1.6, 1.6 Hz, 1H), 5.14 (ddd, *J* = 10.6, 1.5, 1.5 Hz, 1H), 4.22–4.11 (m, 2H), 4.10–4.03 (m, 1H), 2.06–1.98 (m, 1H), 1.81–1.58 (m, 4H), 1.50–1.36 (m, 2H), 1.23–1.10 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 6H).

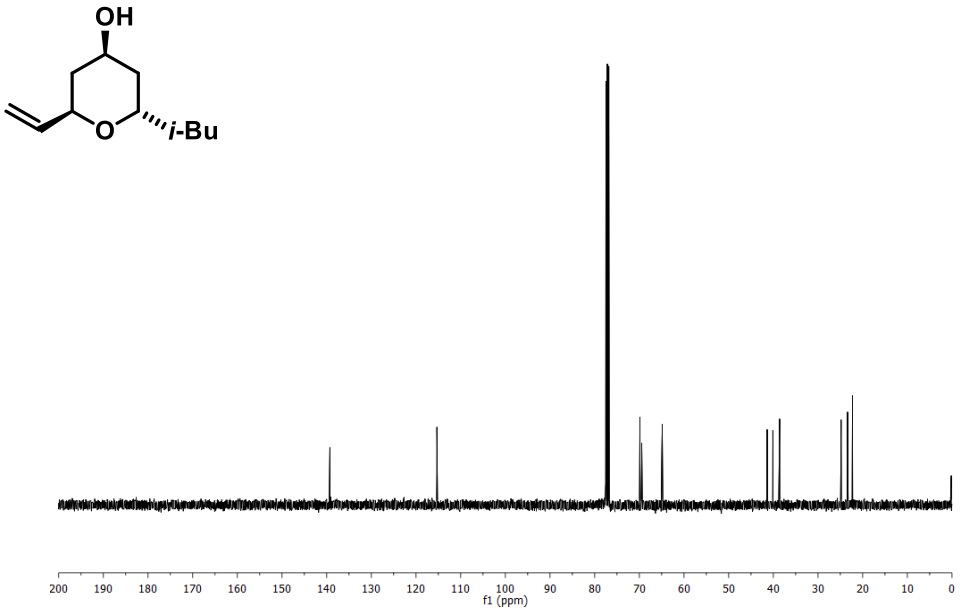
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 115.3, 69.9, 69.5, 64.9, 41.4, 40.1, 38.6, 24.8, 23.4, 22.3.

IR (neat) 3361, 2925, 2868, 1366, 1260, 1024, 920 cm^{-1}.

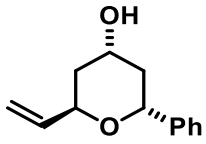
LRMS (ESI+) calcd. for $C_{11}H_{20}O_2Na$ $[M+Na]^+$ 207, found 207.

$[\alpha]^{25}_D$ = –23.09 ° (c = 0.13, $CHCl_3$).


OH
O
i-Bu
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
i-Bu
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*R*,4*S*,6*R*)-2-Phenyl-6-vinyltetrahydro-2H-pyran-4-ol (2,6-*trans*-2.4c).



According to general procedure for Pd-catalyzed *O*-allylation with ***anti*-2.3c** (26.4 mg, 0.10 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (5.2 mg, 0.005 mmol, 5 mol%), and (*R*,*R*)-DPPBA (10.4 mg, 0.015 mmol, 15 mol%) at 50 °C for 18 h, the product **2,6-*trans*-2.4c** was obtained as a colorless oil in 82% yield (28.1 mg, 0.082 mmol, *dr* = 1:1, **2,6-*cis*-2.4c**:**2,6-*trans*-2.4c**) after flash column chromatography (hexanes/EtOAc = 2:1).

According to general procedure for Ir-catalyzed *O*-allylation with ***anti*-2.3c** (39.5 mg, 0.15 mmol, 100 mol%), the product **2,6-*trans*-2.4c** was obtained as a colorless oil in 60% yield (18.3 mg, 0.090 mmol, *dr* = 1:7, **2,6-*cis*-2.4c**:**2,6-*trans*-2.4c**) after flash column chromatography (toluene/EtOAc = 5:1). The unreacted ***anti*-2.3c** was recovered in 26% (10.3 mg, 0.039 mmol). Yield based on recovered starting material (BRSM) was 76%.

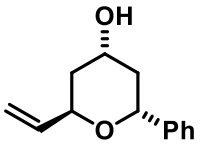
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.24 (m, 5H), 6.00 (ddd, *J* = 17.6, 11.0, 3.8 Hz, 1H), 5.37–5.32 (m, 1H), 5.31–5.28 (m, 1H), 4.83–4.77 (m, 1H), 4.66 (dd, *J* = 11.4, 2.2 Hz, 1H), 4.17–4.04 (m, 1H), 2.25–2.13 (m, 2H), 1.81 (ddd, *J* = 12.6, 11.4, 6.0 Hz, 1H), 1.66–1.48 (m, 2H).

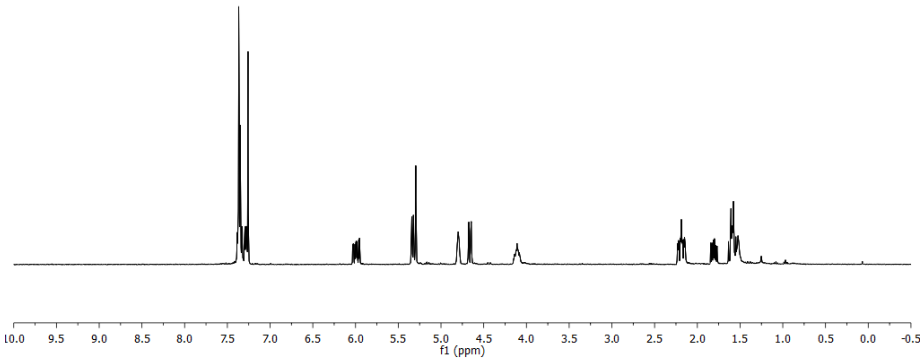
^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 138.0, 128.6, 127.8, 126.2, 117.1, 73.6, 71.8, 64.9, 43.3, 37.2.

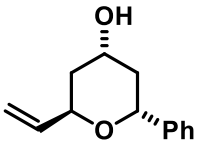
IR (neat) 3362, 2943, 1453, 1409, 1055 cm^{-1}.

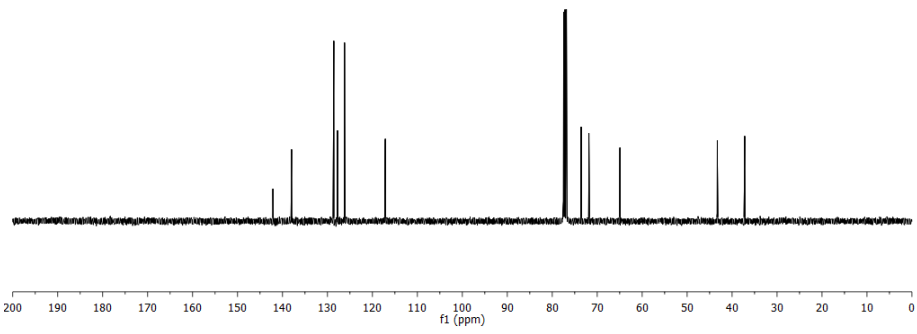
LRMS (CI+) calcd. for $C_{13}H_{17}O_2$ $[M+H]^+$ 205, found 205.

$[\alpha]^{25}_D$ = –10.85 ° (c = 0.43, $CHCl_3$).

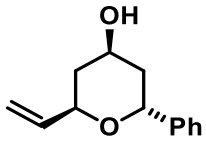

OH
O
Ph


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
Ph


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2*R*,4*R*,6*R*)-2-Phenyl-6-vinyltetrahydro-2H-pyran-4-ol (4-*epi*-2,6-*trans*-2.4c).



According to general procedure for Pd-catalyzed *O*-allylation with ***syn*-2.3c** (26.4 mg, 0.10 mmol, 100 mol%), $Pd_2(dba)_3$-$CHCl_3$ (5.2 mg, 0.005 mmol, 5 mol%), and (*R*,*R*)-DPPBA (10.4 mg, 0.015 mmol, 15 mol%) at 25 °C for 18 h, the product **4-*epi*-2,6-*trans*-2.4c** was obtained as a colorless oil in 95% yield (19.4 mg, 0.095 mmol, *dr* = 2:1, **4-*epi*-2,6-*cis*-2.4c**:**4-*epi*-2,6-*trans*-2.4c**) after flash column chromatography (hexanes/EtOAc = 3:2 to 1:1).

According to general procedure for Ir-catalyzed *O*-allylation with ***syn*-2.3c** (26.4 mg, 0.10 mmol, 100 mol%), the product **4-*epi*-2,6-*trans*-2.4c** was obtained as a colorless oil in 51% yield (10.5 mg, 0.051 mmol, *dr* = 1:4, **4-*epi*-2,6-*cis*-2.4c**:**4-*epi*-2,6-*trans*-2.4c**) after flash column chromatography (hexanes/EtOAc = 4:1 to 1:1). The unreacted ***syn*-2.3c** was recovered in 45% (12.0 mg, 0.045 mmol). Yield based on recovered starting material (BRSM) was 74%.

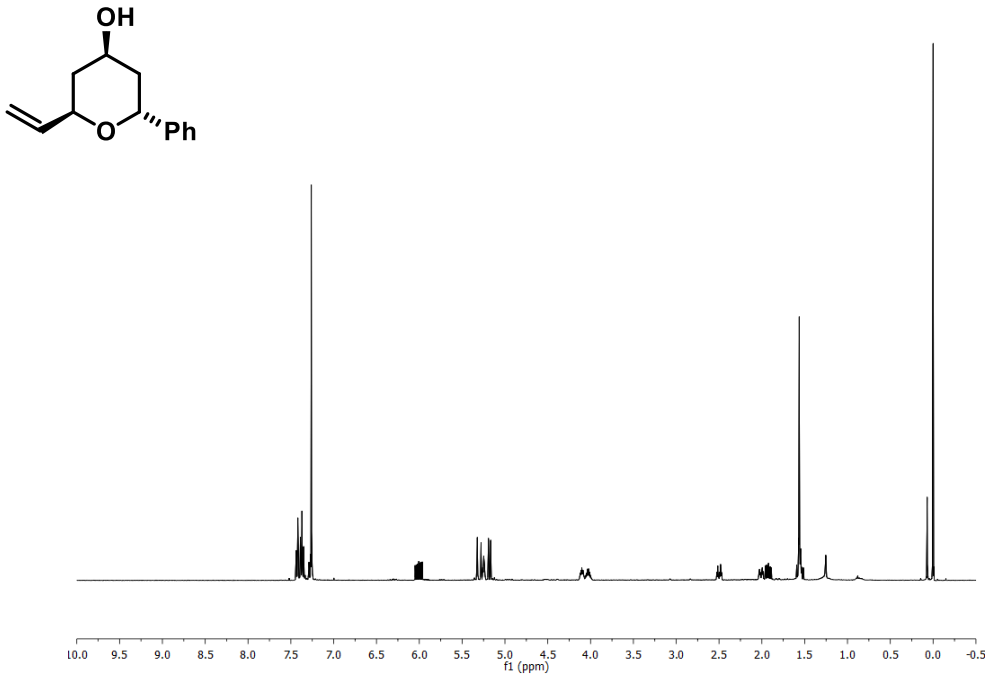
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.17 (m, 5H), 6.01 (ddd, *J* = 17.4, 10.6, 5.2 Hz, 1H), 5.30 (ddd, *J* = 17.4, 1.6, 1.6 Hz, 1H), 5.25 (dd, *J* = 4.5, 4.5 Hz, 1H), 5.18 (ddd, *J* = 10.6, 1.5, 1.5 Hz, 1H), 4.14–4.07 (m, 1H), 4.07–3.97 (m, 1H), 2.50 (dddd, *J* = 13.4, 4.0, 4.0, 1.7 Hz, 1H), 2.07–1.97 (m, 1H), 1.92 (ddd, *J* = 13.4, 9.5, 5.1 Hz, 1H), 1.62–1.48 (m, 2H).

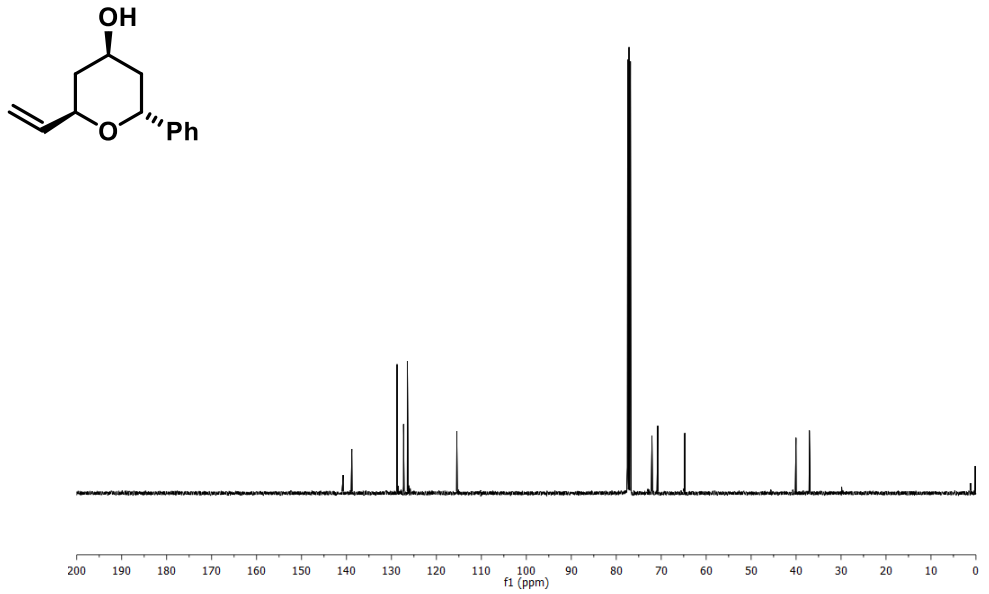
^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 138.8, 128.8, 127.3, 126.5, 115.5, 72.1, 70.8, 64.8, 40.0, 37.0.

IR (neat) 3393, 2923, 2820, 1447, 1363, 1050, 920 cm^{-1}.

LRMS (ESI+) calcd. for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227, found 227.

$[\alpha]^{25}_D$ = +33.33 ° (c = 0.06, $CHCl_3$).


OH
O
Ph
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OH
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Chapter 3: Diastereo- and Enantioselective Iridium Catalyzed Coupling of Vinyl Aziridines with Alcohols: Site-Selective Modification of Unprotected Diols and Synthesis of Substituted Piperidines*

3.1 Introduction

For several years, the Krische group has been interested in redox-triggered iridium catalyzed carbonyl addition *via* transfer hydrogenation, which enables direct primary alcohol C-H functionalization.[1-3] Emanating from this new pattern of reactivity, the enantioselective alcohol C-H allylation,[1] crotylation,[2] and propargylation[3] have been recently developed. Additionally, the cyclometalated π-allyliridium catalysts used in such alcohol C-H functionalization demonstrate a distinct kinetic preference for primary alcohol dehydrogenation,[4] facilitating site-selective C-H functionalization of unprotected diols and triols with high levels of catalyst-directed diastereoselectivity.[5] Taking advantages of these methods, the Krische group has provided the most concise routes towards a number of representative polyketide natural products.[6]

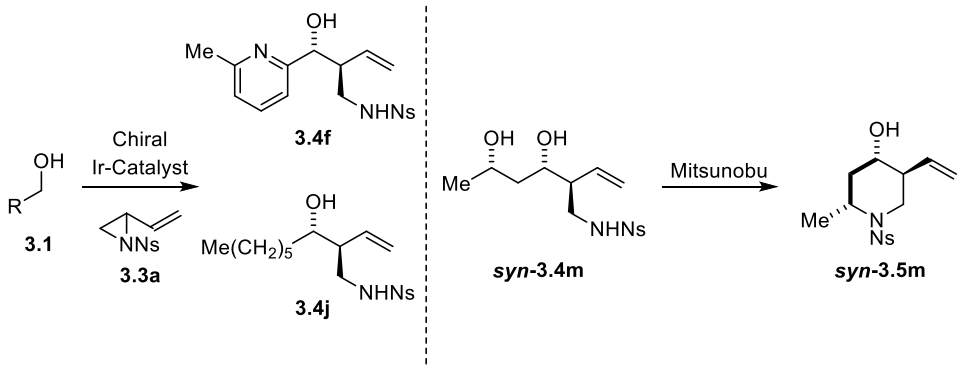
Functionalized piperidines appear frequently as substructures in a number of natural alkaloids and pharmaceutical ingredients.[7] In fact, the piperidine ring is the third most frequently used ring system in small molecule drugs listed in the FDA orange book.[8] Therefore, developing methods to diastereoselectively synthesize piperidine has drawn a great deal of attention.[9]

3.2 Reaction Development and Scope

Here in, we disclose the iridium catalyzed C-C coupling of *N*-(*p*-nitrophenylsulfonyl) protected vinyl aziridine with primary alcohols to furnish products of (α-aminomethyl)allylation with excellent levels of *anti*-diastereo- and enantioselectivity.

* This chapter is based on the published work:
Wang, G.; Franke, J.; Ngo, C. Q.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 7915.

Further, unprotected diols were employed in this transformation to form the diastereomeric products with good isolated yields and high levels of catalyst-directed diastereoselectivity. These products were directly converted to the diastereomeric 2,4,5-trisubstituted piperidines (Scheme 3.1).

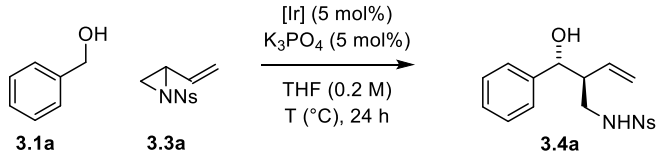


Scheme 3.1 Iridium catalyzed coupling of vinyl aziridine with alcohols: site-selective modification of unprotected diols and synthesis of substituted piperidines.

Because of the competing electrophilic of *O*-allylation of the resulting π-allyliridium complexes,[10] as well as the propensity of vinyl aziridines to participate in metal catalyzed ring expansion, the feasibility of engaging vinyl aziridines in metal catalyzed C-C couplings with primary alcohols was rendered uncertain. Despite these potential liabilities, our initial experiments revealed promising results (Table 3.1). From these results, (*R*)-Ir-3-**VIb**, which incorporates (*R*)-MeO-BIPHEP provided the most favorable results, delivering adduct **3.4a** in 85% yield with a 5:1 *anti*-diastereoselectivity and 96% enantiomeric excess (Table 3.1, entry 15). At lower temperature, a slight improvement in enantiomeric excess was observed, but the isolated yield decreased significantly (Table 3.1, entry 16). Conversely, at higher temperature, conversion improved but stereoselectivity declined (Table 3.1, entry 17). Whereas decreased loadings of vinyl aziridine **3.3a** (100 mol%) diminished the isolated yield of adduct **3.4a** (Table 3.1, entry

18), the use of excessvinyl aziridine **3.3a** (100 mol%) provided adduct **3.4a** in 96% isolated yield with 5:1 *anti*-diastereoselectivity and 97% enantiomeric excess (Table 3.1, entry 19). The use of alternate reaction solvents, such as dioxane or toluene,or omission of potassium phosphate led to substantially diminished yields.

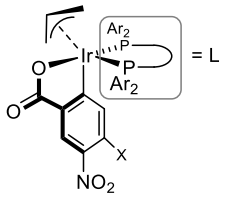
Table 3.1 Selected optimization experiments in the redox-triggered C-C coupling of vinyl aziridine **3.3a** with benzyl alcohol **3.1a** to form *p*-nitrophenylsulfonyl protected amino alcohol **3.4a**.[a]



3.1a (100 mol%) **3.3a** **3.4a**

Entry	3.3a (mol%)	[Ir]	T (°C)	3.4a yield (dr, ee%)
1	200	(*R*)-Ir-3-Ia	60	15% (2:1, 90)
2	200	(*R*)-Ir-3-Ib	60	20% (2:1, 91)
3	200	(*R*)-Ir-3-Ic	60	14% (2:1, 94)
4	200	(*R*)-Ir-3-Id	60	14% (2:1, 91)
5	200	(*R*)-Ir-3-IIa	60	26% (8:1, 91)
6	200	(*R*)-Ir-3-IIb	60	69% (6:1, 90)
7	200	(*R*)-Ir-3-IIc	60	trace conversion
8	200	(*R*)-Ir-3-IIIa	60	28% (4:1, 93)
9	200	(*R*)-Ir-3-IIIb	60	86% (4:1, 90)
10	200	(*R*)-Ir-3-IVa	60	50% (7:1, 84)
11	200	(*R*)-Ir-3-IVb	60	61% (3:1, 95)
12	200	(*R*)-Ir-3-Va	60	28% (3:1, 96)
13	200	(*R*)-Ir-3-Vb	60	65% (3:1, 94)
14	200	(*R*)-Ir-3-VIa	60	51% (5:1, 96)
15	200	(*R*)-Ir-3-VIb	60	85% (5:1 96)
16	200	(*R*)-Ir-3-VIb	45	70% (5:1 97)
17	200	(*R*)-Ir-3-VIb	80	88% (2:1 85)
18	100	(*R*)-Ir-3-VIb	60	36% (5:1 95)
⇨ 19	300	(*R*)-Ir-3-VIb	60	96% (5:1 97)

[a]Yields are of material isolated by silica gel chromatography.

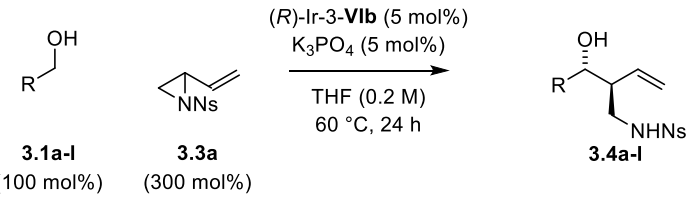


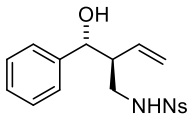
(*R*)-Ir-3-Ia, L = (*R*)-BINAP, X = H
(*R*)-Ir-3-Ib, L = (*R*)-BINAP, X = CN
(*R*)-Ir-3-Ic, L = (*R*)-Tol-BINAP, X = CN
(*R*)-Ir-3-Id, L = (*R*)-Xylyl-BINAP, X = CN
(*R*)-Ir-3-IIa, L = (*R*)-SEGPHOS, X = H
(*R*)-Ir-3-IIb, L = (*R*)-SEGPHOS, X = CN
(*R*)-Ir-3-IIc, L = (*R*)-DM-SEGPHOS, X = CN
(*R*)-Ir-3-IIIa, L = (*R*)-SYNPHOS, X = Cl
(*R*)-Ir-3-IIIb, L = (*R*)-SYNPHOS, X = CN
(*R*)-Ir-3-IVa, L = (*R*)-C3-TUNEPHOS, X = Cl
(*R*)-Ir-3-IVb, L = (*R*)-C3-TUNEPHOS, X = CN
(*R*)-Ir-3-Va, L = (*R*)-Cl,MeO-BIPHEP, X = Cl
(*R*)-Ir-3-Vb, L = (*R*)-Cl,MeO-BIPHEP, X = CN
(*R*)-Ir-3-VIa, L = (*R*)-MeO-BIPHEP, X = Cl
(*R*)-Ir-3-VIb, L = (*R*)-MeO-BIPHEP, X = CN

The scope of the iridium catalyzed (α-aminomethyl)allylation was tested with diverse primary alcohols **3.1a-3.1l** (100 mol%) and vinyl aziridine **3.3a** (300 mol%) under the condition of (*R*)-Ir-3-**VIb** (5 mol%) and substoichiometric potassium phosphate (5 mol%) in THF (0.2 M) at 60 °C (Table 3.2). As illustrated in the conversion of **3.1a-3.1f**

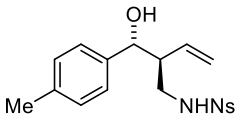
to **3.4a-3.4f**, a range of benzylic alcohols participate in C-C coupling, including alcohol **3.1f**, which incorporates a Lewis basic pyridyl-substituent. Cinnamyl alcohol **3.1g**, prenyl alcohols **3.1h** and geraniol **3.1i** are transformed to adducts **3.4g-3.4i**, illustrating use of allylic alcohols as coupling partners. Finally, as demonstrated by the conversion of heptanol **3.1j**, *O*-benzyl 1,3-propane diol **3.1k** and cyclopropyl methanol **3.1l** to adducts **3.4j-3.4l**, respectively, aliphatic alcohols participate in coupling. In each case examined, good to excellent yields, good *anti*-diastereoselectivities and uniformly high enantioselectivities were observed.

Table 3.2 Regio- diastereo- and enantioselective iridium catalyzed (α-aminomethyl)allylation of alcohols **3.1a-3.1l** with vinyl aziridine **3.3a**.[a]

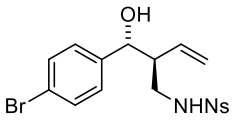




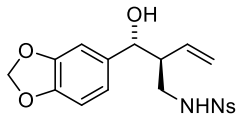
3.4a, 96% Yield
5:1 *dr*, 97% *ee*



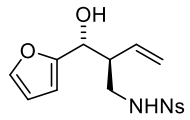
3.4b, 70% Yield
5:1 *dr*, 94% *ee*
(X-ray)



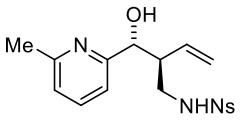
3.4c, 90% Yield
4:1 *dr*, 96% *ee*



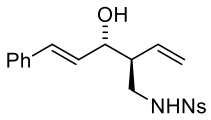
3.4d, 73% Yield
4:1 *dr*, 96% *ee*



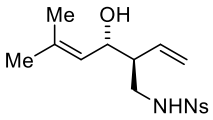
3.4e, 73% Yield
10:1 *dr*, 97% *ee*



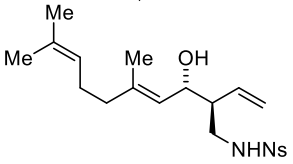
3.4f, 78% Yield
5:1 dr, 97% *ee*[b]



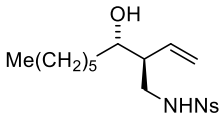
3.4g, 73% Yield
6:1 dr, 95% ee



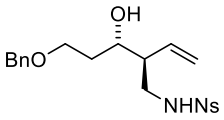
3.4h, 70% Yield
8:1 *dr*, 95% *ee*



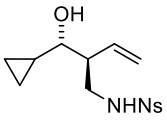
3.4i, 67% Yield
9:1 *dr*, 94% *ee*[b]



3.4j, 96% Yield
6:1 *dr*, 99% *ee*



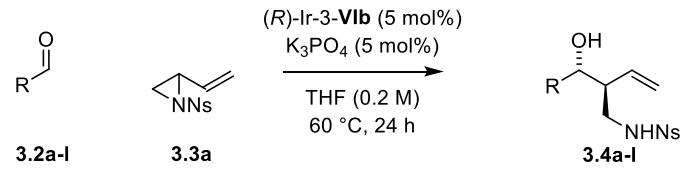
3.4k, 87% Yield
8:1 *dr*, 98% *ee*



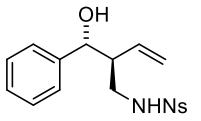
3.4l, 64% Yield
4:1 *dr*, 95% *ee*

[a]Yields are of material isolated by silica gel chromatography. [b]48 h.

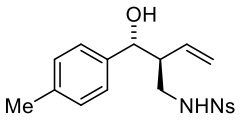
Table 3.3 Regio- diastereo- and enantioselective iridium catalyzed (α-aminomethyl)allylation of aldehydes **3.2a-3.2l** with vinyl aziridine **3.3a**.[a]



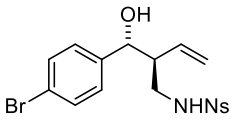
3.2a-l (100 mol%) **3.3a** (300 mol%) **3.4a-l**



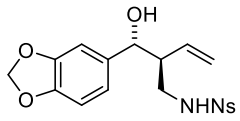
3.4a, 80% Yield
5:1 dr, 95% ee



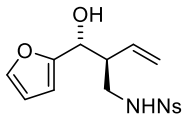
3.4b, 72% Yield
4:1 dr, 96% ee
(X-ray)



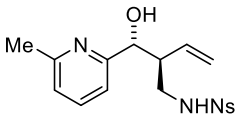
3.4c, 86% Yield
4:1 dr, 97% ee



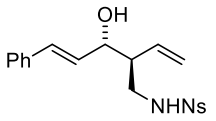
3.4d, 87% Yield
4:1 dr, 97% ee



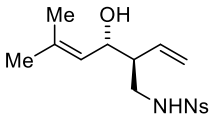
3.4e, 85% Yield
9:1 dr, 97% ee



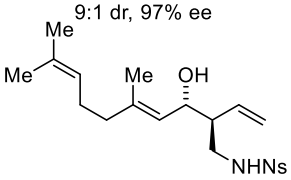
3.4f, 72% Yield
4:1 dr, 96% ee



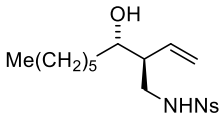
3.4g, 77% Yield
5:1 dr, 98% ee



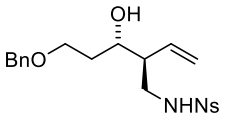
3.4h, 96% Yield
7:1 dr, 99% ee



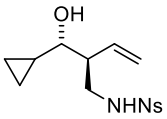
3.4i, 66% Yield
8:1 dr, 91% ee



3.4j, 90% Yield
5:1 dr, 96% ee



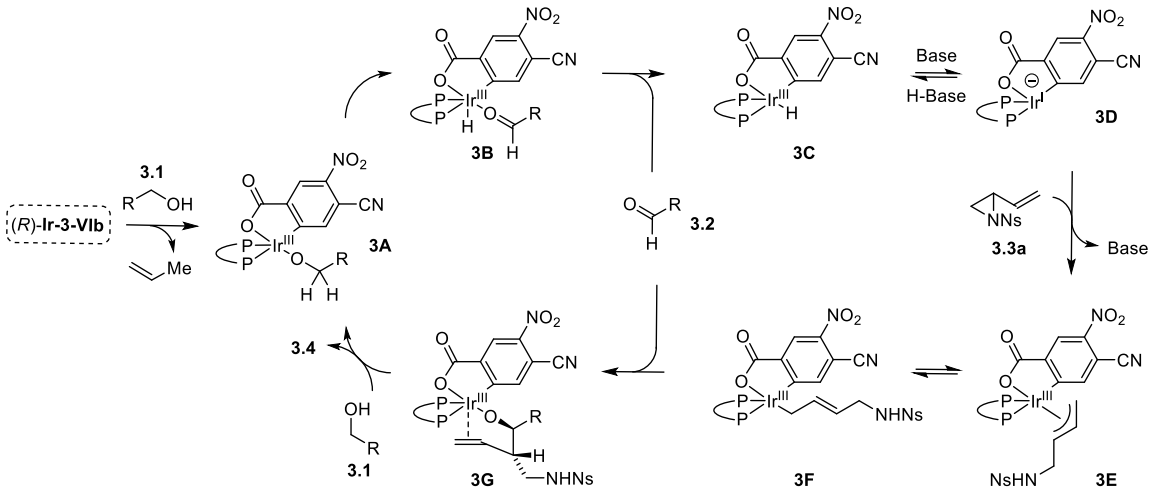
3.4k, 85% Yield
7:1 dr, 95% ee



3.4l, 63% Yield
4:1 dr, 98% ee

[a]Yields are of material isolated by silica gel chromatography.

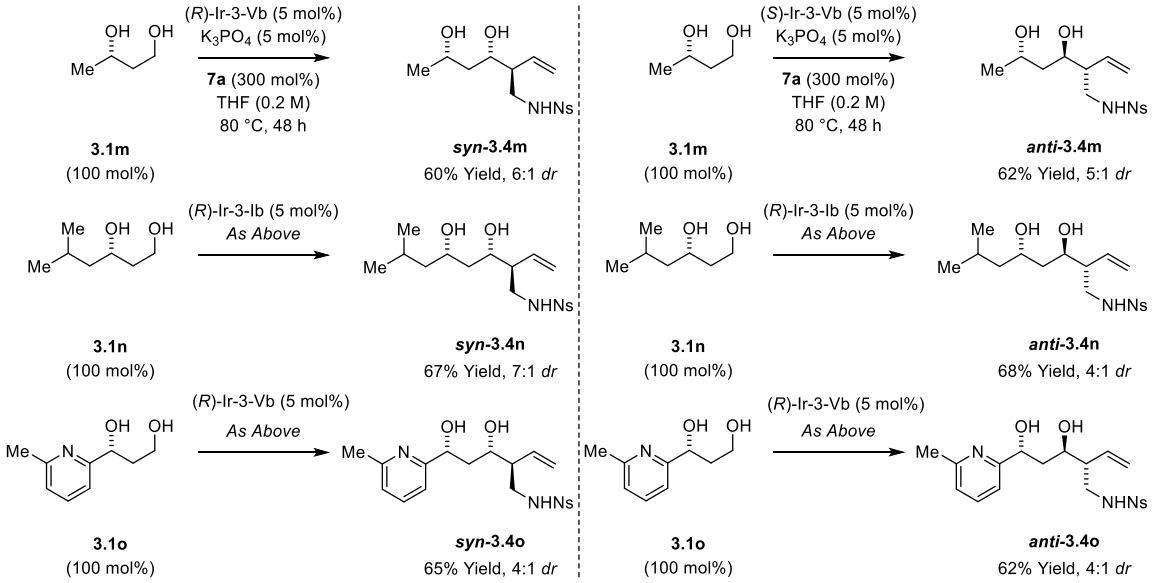
Related reductive couplings of vinyl aziridine **3.3a** with aldehydes **3.4a-3.4l** also were evaluated (Table 3.3). By using 2-propanol (300 mol%) as terminal reductant, similar as alcohols, good to excellent yields, good *anti*-diastereoselectivities and uniformly high enantioselectivities were observed in the coupling reactions. The absolute configuration of adducts **3.4a-l** was made in analogy to the structural assignment of adducts **3.4b**, which was determined by single crystal x-ray diffraction analysis. Based on the collective data,[11] a general catalytic mechanism accounting for the reaction of primary alcohols **3.1a-l** with vinyl aziridines **3.3a** to form adducts **3.4a-l** is given (Scheme 3.2).



Scheme 3.2 General catalytic mechanism for iridium catalyzed (α-aminomethyl)allylation of alcohols **3.1a-l** with vinyl aziridine **3.3a**.

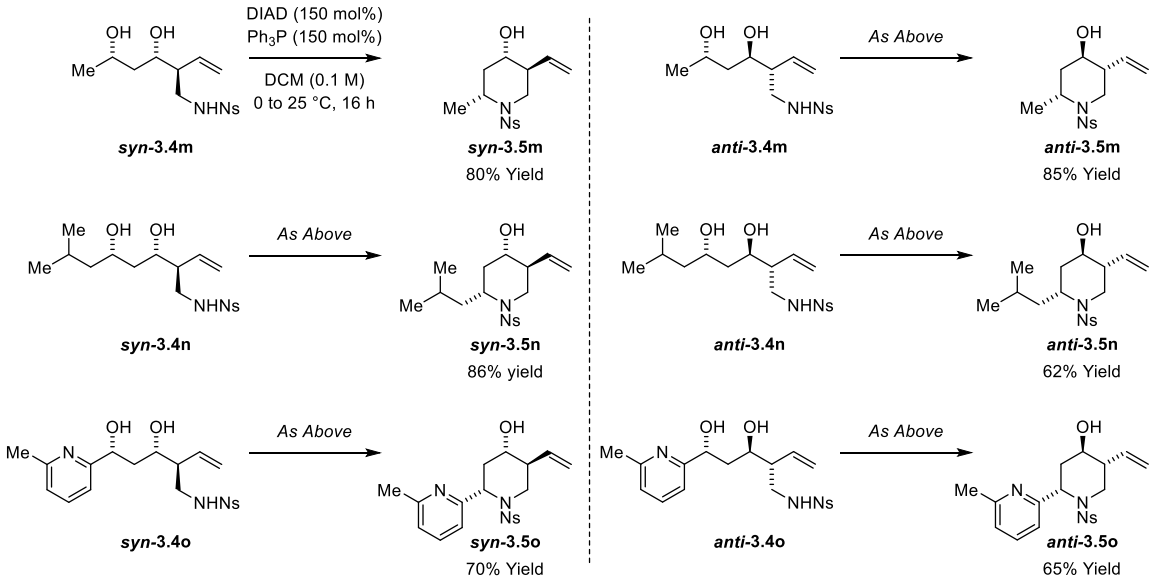
Having demonstrated the feasibility and scope of the coupling of primary alcohols **3.1a**−**3.1l**, the catalyst-directed diastereo- and site-selective C-C coupling of unprotected diols **3.1m-3.1o** with vinyl aziridine **3.3a** was investigated (Table 3.4). Different from aforementioned alcohols, the coupling reactions of unprotected diols with aziridine **3.3a** required longer reaction time. In addition, the catalysts used in these transformations were case dependant. Specifically, in the coupling of diol **3.1m** or **3.1o** with vinyl aziridines **3.3a**, the iridium catalyst (*R*)-Ir-3-**Vb**, which is modified by (*R*)-Cl,MeO-BIPHEP, gave slightly better results than catalyst (*R*)-Ir-3-**VIb**, which is modified by (*R*)-MeO-BIPHEP. However, for diol **3.1n**, the BINAP modified catalyst (*R*)-Ir-3-**Ib** provided the best results. In a parallel set of experiments, the unprotected diols **3.1m-3.1o** were reacted with the respective enantiomeric iridium catalysts. The diastereomeric adducts *anti*-**3.4m,** *anti*-**3.4n** and *anti*-**3.4o** also were formed in good yields with similar levels catalyst-directed diastereoselectivity.

Table 3.4 Catalyst-directed diastereo- and site-selectivity in the iridium catalyzed (α-aminomethyl)allylation of unprotected 1,3-diols **3.1m-o** with vinyl aziridine **3.3a**.[a]



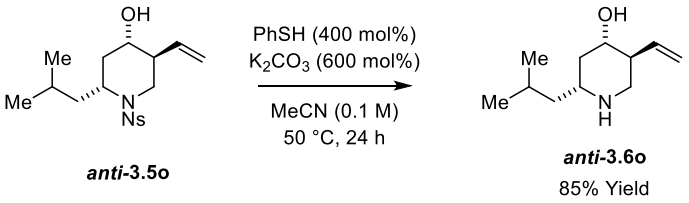
[a]Yields are of material isolated by silica gel chromatography.

Table 3.5 Conversion of *syn*-**3.4m-o** and *anti*-**3.4m-o** to diastereomeric 2,4,5-trisubstituted piperidines *syn*-**3.5m-o** and *anti*-**3.5m-o**.[a]



[a]Yields are of material isolated by silica gel chromatography.

With the diol coupling products *syn*-**3.4m,** *syn*-**3.4n** and *syn*-**3.4o** in hand, Mitsunobu reaction conditions[12] was applied to convert the coupling products to 2,4,5-trisubstituted piperidines (Table 3.5). Cyclization proceeded most efficiently using DIAD (disisopropyl azodicarboxylate), delivering the 2,4,5-trisubstituted piperidines *syn*-**3.5m**, *syn*-**3.5n** and *syn*-**3.5o** as single stereoisomers. Similarly, under Mitsunobu conditions, the diol coupling products *anti*-**3.4m,** *anti*-**3.4n** and *anti*-**3.4o** were converted to the diastereomeric 2,4,5-trisubstituted piperidines *anti*-**3.5m**, *anti*-**3.5n** and *anti*-**3.5o**. In all cases, cyclization proceeded with complete inversion of the carbinol stereocenter in good to excellent yield. Finally, as illustrated in the conversion of piperidine *anti*-**3.5o** to the free secondary amine *anti*-**3.6o**, the experiments will be carried out to remove *N*-(*p*-nitrophenylsulfonyl) protecting group[13] (Scheme 3.3).



***anti*-3.5o** **anti-3.6o** 85% Yield

Scheme 3.3 Cleavage of *N*-(*p*-nitrophenylsulfonyl) protecting group.

3.3 CONCLUSION

The first enantioselective umpoled allylations of aldehydes with vinyl aziridines to form products of carbonyl (α-aminomethyl)allylation were developed. These processes may be conducted in an equally efficient manner from the alcohol oxidation level or from the aldehyde oxidation level, delivering products of C-C bond formation in good to excellent yield, good levels of *anti*-diastereoselectivity and uniformly high levels of enantioselectivity. Further, the unprotected chiral diols **3.1m**-**3.1n** could be employed in this transformation to provide the diastereomeric products of *C*-allylation *syn*-**3.4m**, *syn*-

3.4n and *syn*-**3.4o** and *anti*-**3.4m,** *anti*-**3.4n**, *anti*-**3.4o** with good isolated yields and good catalyst-directed diastereoselectivity, which enables concise approach to 2,4,5-trisubstituted piperidines.

3.4 Experimental Details

General Information

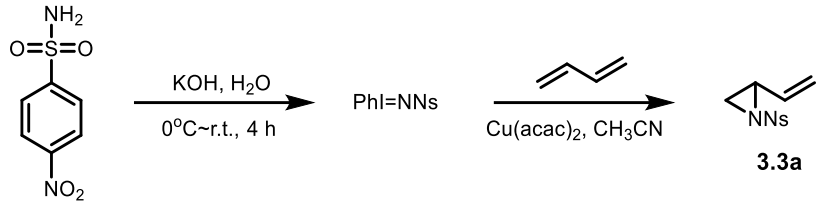
All reactions were run under an atmosphere of argon. Sealed tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator. Tetrahydrofuran, toluene, and dioxane were distilled from sodium-benzophenone immediately prior to use. Dichloromethane was distilled from calcium hydride under a nitrogen atmosphere prior to use. Anhydrous solvents were transferred by oven-dried syringes. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F254). Visualization was accomplished with UV light followed by dipping in *p*-anisaldehyde stain solution then heating. Purification of reactions was carried out by flash chromatography using Silacycle silica gel (40-63 μm, unless indicated specifically). Potassium phosphate was purchased through Acros Organics, flame dried prior to use, and stored in a desiccator. Substrates **3.1k**, **3.2i** and **3.2k** were prepared through known procedures..All other alcohols and aldehydes were used from commercially available sources, and purified prior to use.

Spectroscopy, Spectrometry, and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). High-resolution mass spectra (HRMS) were obtained on an Agilent Technologies 6530 Accurate Mass Q-TOF LC/MS instrument and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M, M+H, or M-H), or a suitable fragment ion. 1H nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δH (7.26 ppm). ^{13}C nuclear magnetic resonance spectra were recorded

using a 100 MHz spectrometer for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CDCl_3$ δC (77.16 ppm).

Synthesis of Vinyl Aziridine 3.3a



The first step was done follow the reported procedure.[14]

To a solution of PhI=NNs (6.4 mmol) in CH_3CN 10 ml in a sealed tube at -78 °C, $Cu(acac)_2$ (1.3 mmol) was added. Then freshly condensed 1, 3-butadiene (1.8 mL, 19.3 mmol) was added into the tube. The resulting mixture was allowed to stir at R.T. for 2 h. The reaction mixture was concentrated *in vacuo* and the crude residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 6:1) to furnish the 1-((4-nitrophenyl)sulfonyl)-2-vinylaziridine **3.3a** as an off white solid in 37% yield. Data is consistent with that reported in the literature.[15]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.0 Hz, 2H), 8.16 (d, *J* = 9.0 Hz, 2H), 5.58–5.43 (m, 2H), 5.33–5.27 (m, 1H), 3.43–3.36 (m, 1H), 2.92 (d, *J* = 7.1 Hz, 1H), 2.34 (d, *J* = 4.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 144.2, 132.3, 129.2, 124.5, 121.3, 42.0, 34.9.

General Procedure and Spectral Data for Coupling of Vinyl Aziridine and Alcohols (3.1a-3.1l) or Aldehydes (3.2a-3.2l)

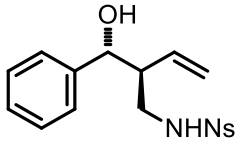
*General Procedure for Coupling of Vinyl Aziridine (**3.3a**) and Alcohols (**3.1a-3.1l**)*

A flame-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (1.1 mg, 0.005 mmol, 5 mol%), (*R*)-Ir-3-**VIb** (5.0 mg, 0.005 mmol, 5 mol%), alcohol (0.10 mmol, 100 mol%) and 1-((4-nitrophenyl)sulfonyl)-2-vinylaziridine **3.3a** (76.3 mg, 0.30 mmol, 300 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.5 mL, 0.2 M) was added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 60 ºC for 24 h. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography to furnish the title compound.

*General Procedure for Coupling of Vinyl Aziridine (**3.3a**) and Aldehydes (**3.2a-3.2l**)*

A flame-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (1.08 mg, 0.005 mmol, 5 mol%), (*R*)-Ir-3-**VIb** (5.0 mg, 0.005 mmol, 5 mol%), aldehyde (0.1 mmol, 100 mol%) and 1-((4-nitrophenyl)sulfonyl)-2-vinylaziridine **3.3a** (76.3 mg, 0.3 mmol, 300 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.5 mL, 0.2 M) and 2-propanol (18.0 mg, 0.3 mmol, 300 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 60 ºC for 24 h. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography to furnish the title compound.

***N*-((*S*)-2-((*R*)-hydroxy(phenyl)methyl)but-3-en-1-yl)-4-nitrobenzenesulfonamide (3.4a)**



<u>*From alcohol oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with benzyl alcohol (10.8 mg, 0.1 mmol, 100 mol%), the product **3.4a** was obtained as gel in 96% yields (34.8 mg, 0.096 mmol, *anti:syn*=5:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). <u>*From aldehyde oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with benzaldehyde (10.6 mg, 0.1 mmol, 100 mol%), the product **3.4a** was obtained as gel in 80% yields (29.0 mg, 0.080 mmol, *anti:syn*=5:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

<u>^{1}H NMR (400 MHz, $CDCl_3$)</u> δ 8.34 (d, *J* = 9.0 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.35–7.27 (m, 3H), 7.23–7.17 (m, 2H), 5.58 (ddd, *J* = 17.2, 10.4, 8.9 Hz, 1H), 5.19 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.08–5.00 (m, *J* = 17.2, 1.3, 0.8 Hz, 2H), 4.72 (dd, *J* = 5.3, 3.1 Hz, 1H), 3.11 (ddd, *J* = 13.2, 7.0, 6.3 Hz, 1H), 2.96 (ddd, *J* = 12.7, 7.6, 4.8 Hz, 1H), 2.58–2.46 (m, 1H), 2.20 (d, *J* = 3.2 Hz, 1H).

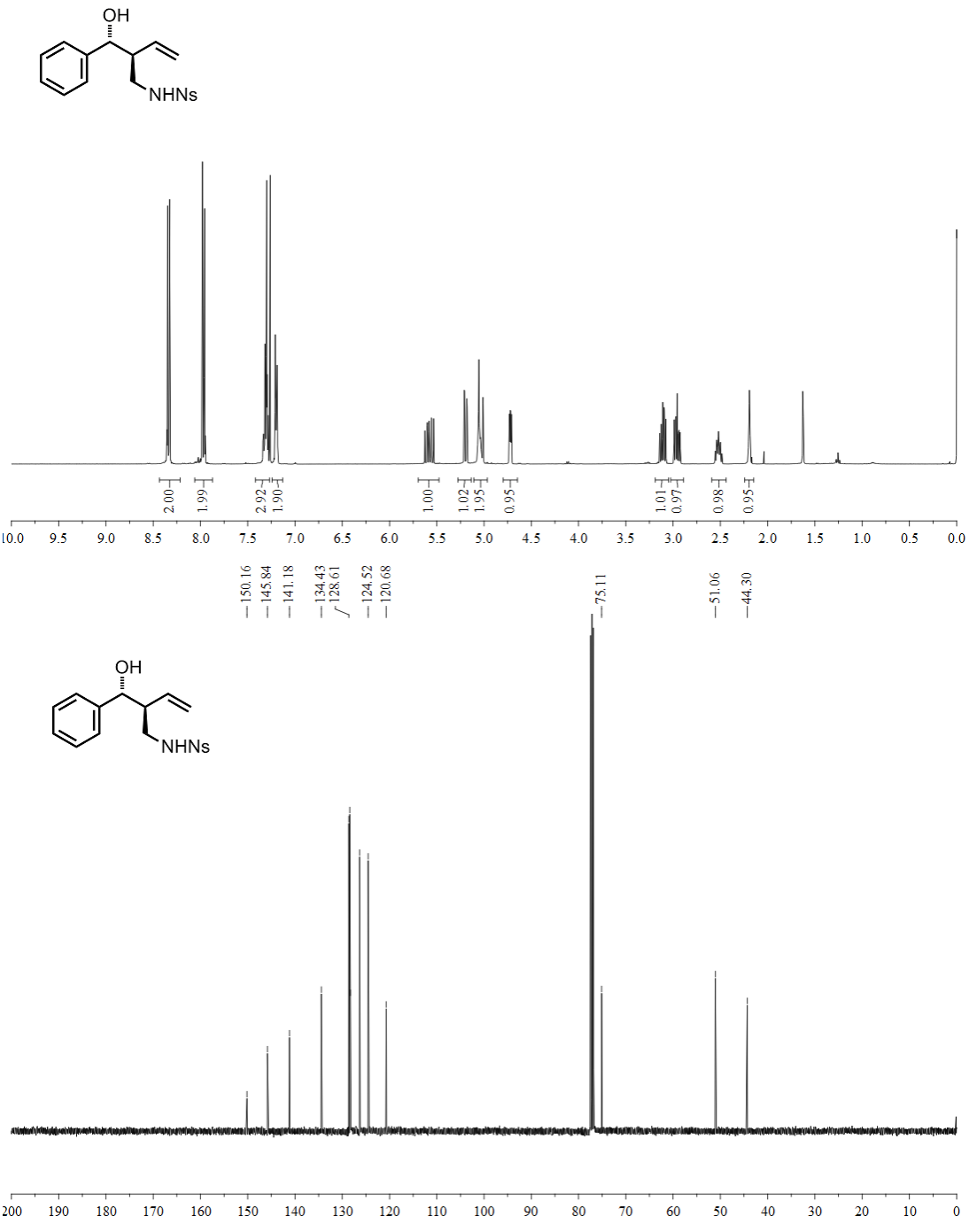
<u>^{13}C NMR (100 MHz, $CDCl_3$)</u> δ 150.2, 145.8, 141.2, 134.4, 128.6, 128.4, 128.3, 126.4, 124.5, 120.7, 75.1, 51.1, 44.3.

<u>LRMS</u> (ESI) Calcd. for $C_{17}H_{18}N_2O_5SNa$ $[M+Na]^+$: 385.1, Found: 385.1.

<u>FTIR</u> (neat): 2925, 2410, 1540, 1349, 1164, 1092, 855 cm^{-1}.

<u>HPLC</u>: (Chiralcel AD-H column, hexanes:*i*-PrOH = 80:20, 1.00 mL/min, 254 nm), *ee* =97% from benzyl alcohol, *ee* = 95% from benzaldehyde.

<u>$[\alpha]^{20}_D$ =</u> +15.60 ° (c 0.30, $CHCl_3$).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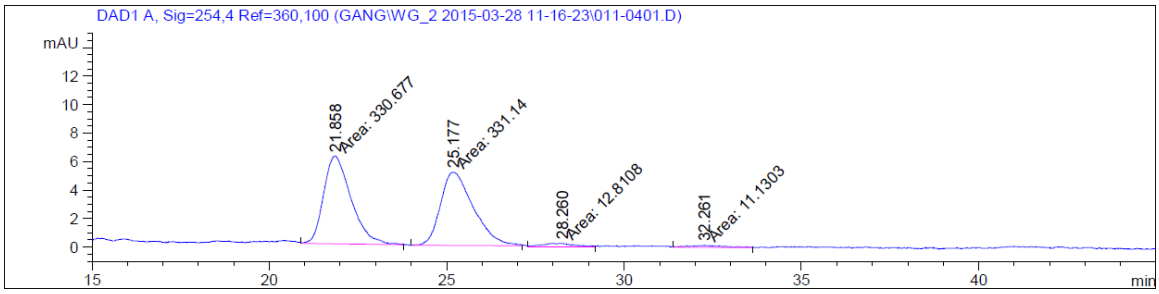
1.99
2.92
1.90
1.00
1.02
1.95
0.95
1.01
0.97
0.98
0.95
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
150.16
145.84
141.18
134.43
128.61
124.52
120.68
75.11
51.06
44.30
OH
NHNs
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



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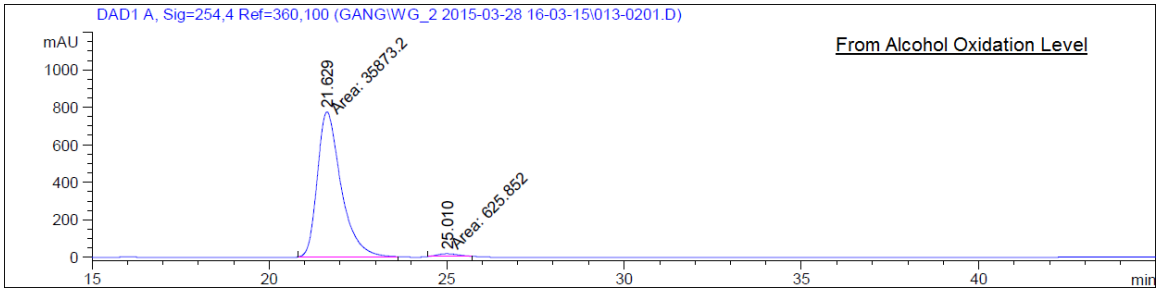
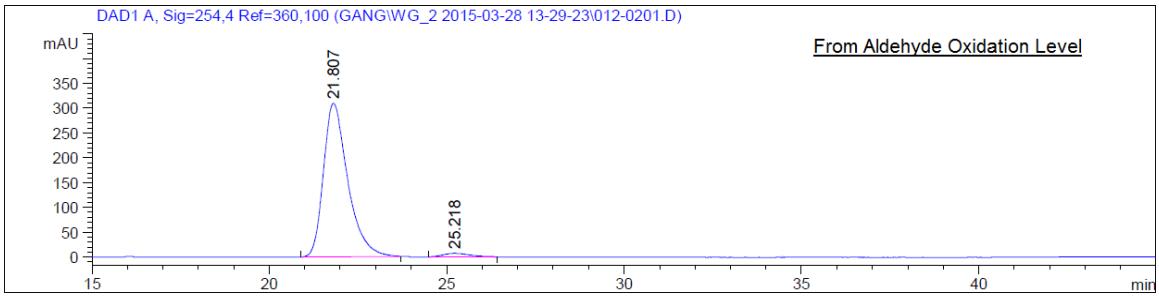
2	25.177	MM	1.0723	331.14020	5.14698	48.2882
3	28.260	MM	0.9228	12.81080	2.31380e-1	1.8681
4	32.261	MM	1.2279	11.13033	1.51077e-1	1.6231
Totals :				685.75794	11.68739	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.629	MF	0.7726	3.58732e4	773.90808	98.2853
2	25.010	FM	0.6798	625.85229	15.34365	1.7147
Totals :				3.64991e4	789.25173	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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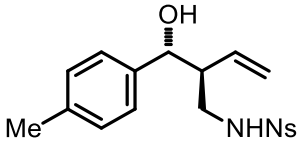
2	25.218	BB	0.6515	384.32416	7.38048	2.5351
Totals :				1.51604e4	316.77119	

***N*-((*S*)-2-((*R*)-hydroxy(p-tolyl)methyl)but-3-en-1-yl)-4-nitrobenzenesulfonamide (3.4b)**



<u>*From alcohol oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with 4-methylbenzyl alcohol (12.2 mg, 0.1 mmol, 100 mol%), the product **3.4b** was obtained as white solid in 70% yields (26.4 mg, 0.070 mmol, *anti:syn*=5:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). <u>*From aldehyde oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with p-tolualdehyde (12.0 mg, 0.1 mmol, 100 mol%), the product **3.4b** was obtained as white solid in 72% yields (27.1 mg, 0.072 mmol, *anti:syn*=4:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

<u>^{1}H NMR (400 MHz, $CDCl_3$)</u> δ 8.34 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 5.57 (ddd, *J* = 17.2, 10.3, 8.9 Hz, 1H), 5.20 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.11–5.00 (m, 2H), 4.66 (d, *J* = 5.4 Hz, 1H), 3.09 (dt, *J* = 13.0, 6.6 Hz, 1H), 2.93 (ddd, *J* = 12.6, 7.5, 4.8 Hz, 1H), 2.56–2.44 (m, 1H), 2.34 (s, 3H), 2.13 (brs, 1H).

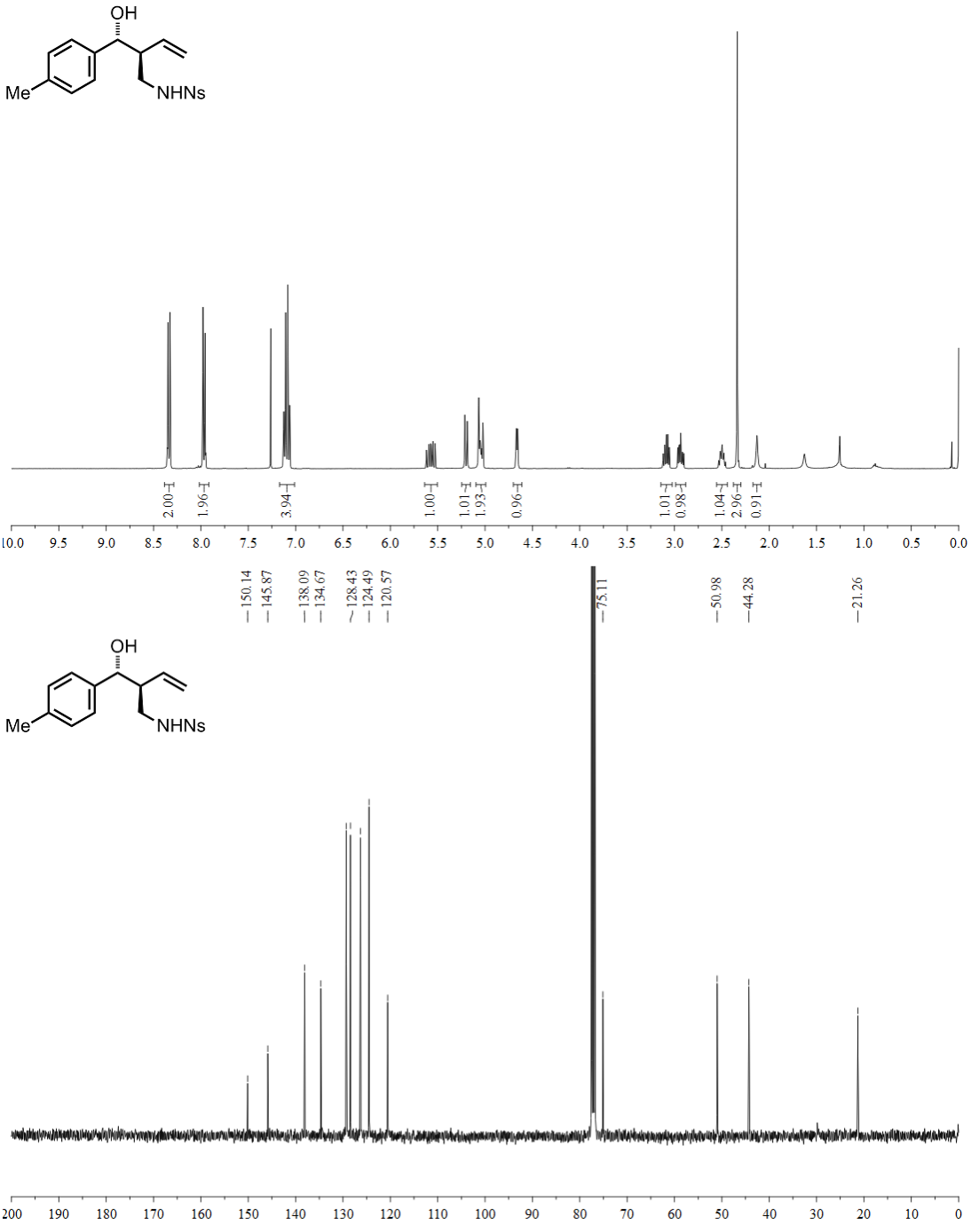
<u>^{13}C NMR (100 MHz, $CDCl_3$)</u> δ 150.1, 145.9, 138.1, 134. 7, 129.3, 128.4, 126.3, 124.5, 120.6, 75.1, 50.9, 44.3, 21.3.

<u>LRMS</u> (ESI) Calcd. for $C_{18}H_{20}N_2O_5SNa$ $[M+Na]^+$: 399.1, Found: 399.1.

<u>FTIR</u> (neat): 3302, 2922, 2411, 1529, 1402, 1348, 1093, 854 cm^{-1}.

<u>HPLC</u>: (Chiralcel AD-H column, hexanes:*i*-PrOH = 93:07, 1.00 mL/min, 254 nm), *ee* =94% from 4-methylbenzyl, *ee* = 96% from p-tolualdehyde.

<u>$[\alpha]^{20}_D$ =</u> +7.14 ° (c 0.70, $CHCl_3$). **<u>mp</u>**: 105-107 ºC.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Me
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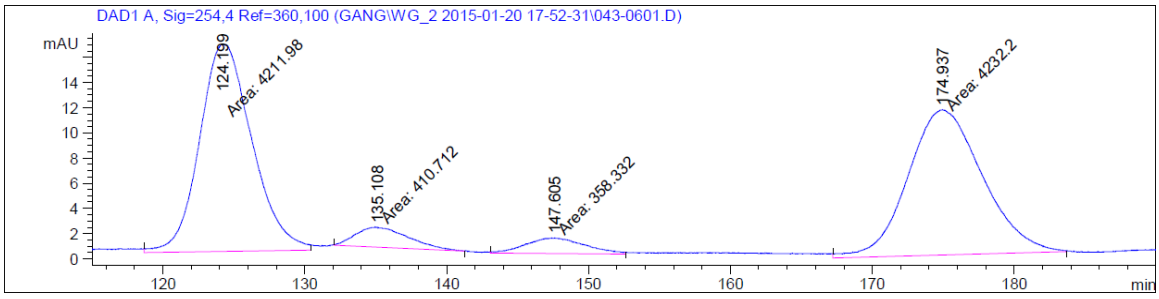
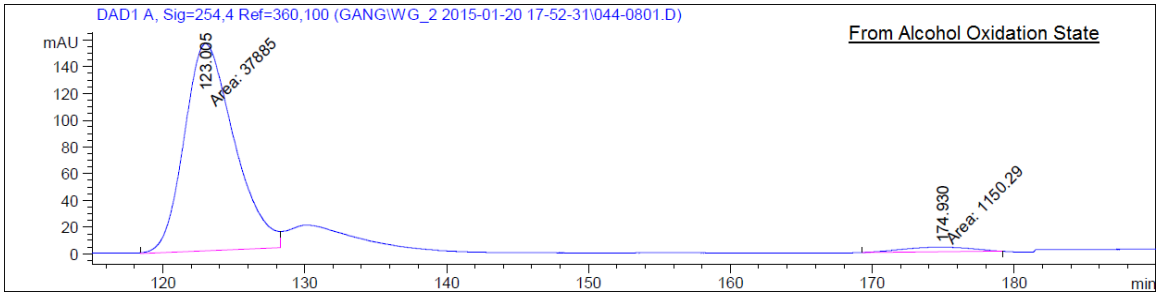
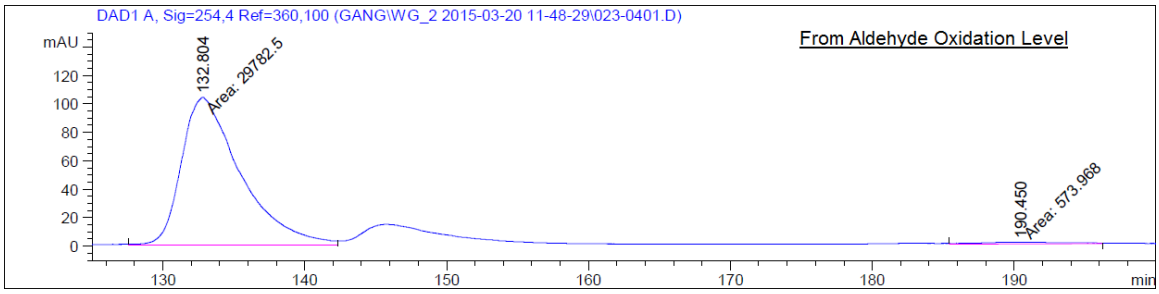
1.96
3.94
1.00
1.01
1.93
0.96
1.01
0.98
1.04
2.96
0.91
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
150.14
145.87
138.09
134.67
128.43
124.49
120.57
75.11
50.98
44.28
21.26
OH
Me
NHNs
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	124.199	MM	4.2712	4211.98145	16.43560	45.7167
2	135.108	MM	4.3162	410.71246	1.58593	4.4579
3	147.605	MM	4.8550	358.33249	1.23010	3.8893
4	174.937	MM	6.1059	4232.20459	11.55224	45.9362
Totals :				9213.23099	30.80387	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	123.005	MM	4.0626	3.78850e4	155.42126	97.0532
2	174.930	MM	5.4783	1150.29004	3.49956	2.9468
Totals :				3.90353e4	158.92082	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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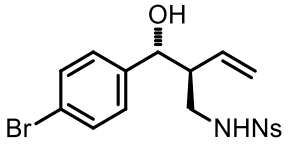
2	190.450	MF	7.1310	573.96777	1.34148	1.8908
Totals :				3.03565e4	104.86296	

***N*-((*S*)-2-((*R*)-(4-bromophenyl)(hydroxy)methyl)but-3-en-1-yl)-4-nitrobenzenesulfonamide (3.4c)**



<u>*From alcohol oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with 4-bromobenzyl alcohol (18.7 mg, 0.1 mmol, 100 mol%), the product **3.4c** was obtained as gel in 90% yields (39.7 mg, 0.090 mmol, *anti:syn*=4:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). <u>*From aldehyde oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with 4-bromobenzaldehyde (18.5 mg, 0.1 mmol, 100 mol%), the product **3.4c** was obtained as gel in 86% yields (37.9 mg, 0.086 mmol, *anti:syn*=4:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

<u>^{1}H NMR (400 MHz, $CDCl_3$)</u> δ 8.36 (d, *J* = 9.0 Hz, 2H), 8.00 (d, *J* = 9.0 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 5.57 (ddd, *J* = 17.3, 10.4, 8.9 Hz, 1H), 5.19 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.07–4.94 (m, 2H), 4.80–4.75 (m, 1H), 3.15 (ddd, *J* = 12.9, 7.4, 6.5 Hz, 1H), 3.01–2.92 (m, 1H), 2.50 (dt, *J* = 13.7, 7.0 Hz, 1H), 2.24 (d, *J* = 3.4 Hz, 1H).

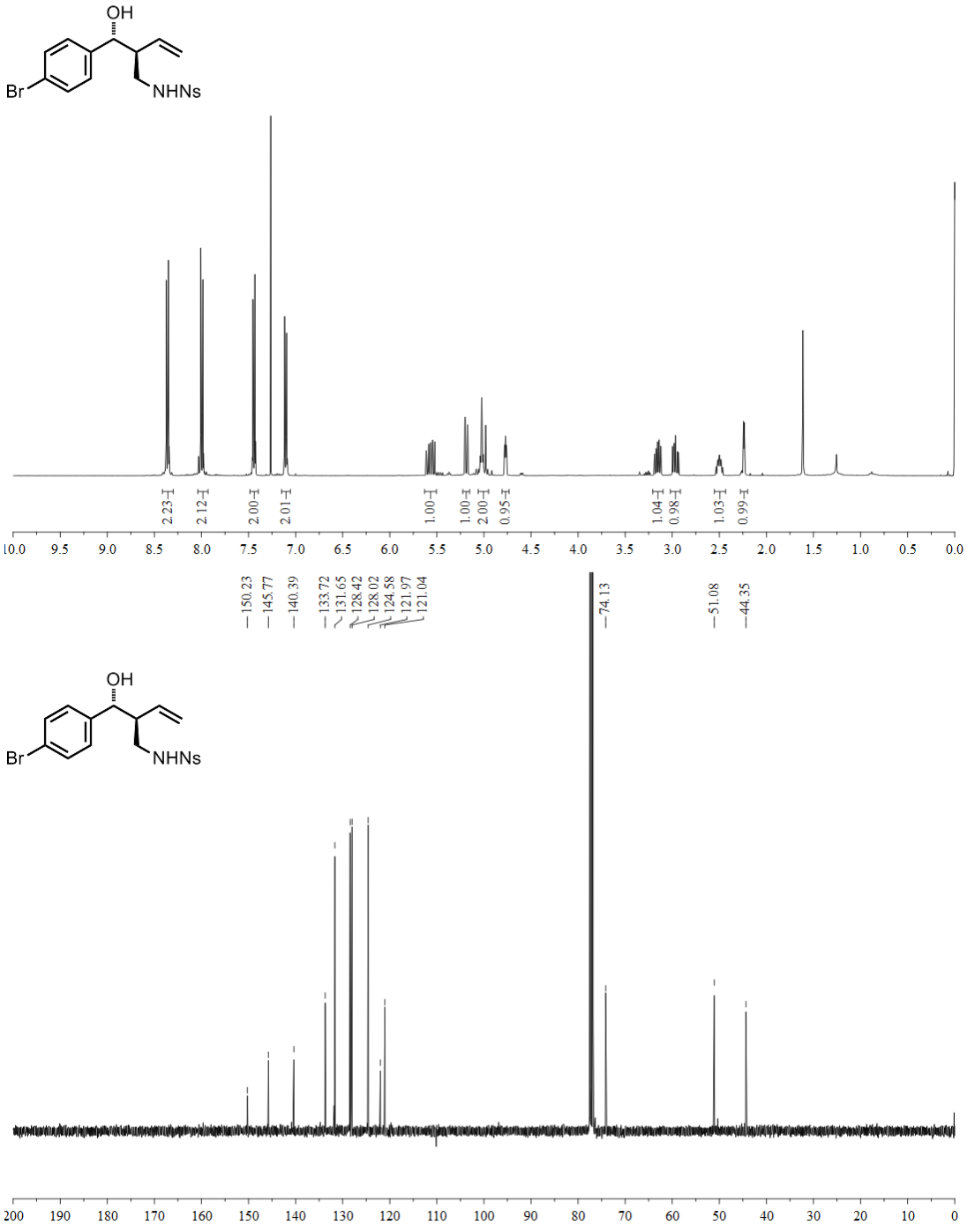
<u>^{13}C NMR (100 MHz, $CDCl_3$)</u> δ 150.2, 145.8, 140.4, 133.7, 131.7, 128.4, 128.02, 124.6, 121.9, 121.0, 74.1, 51.1, 44.4.

<u>LRMS</u> (ESI) Calcd. for $C_{17}H_{17}BrN_2O_5SNa$ $[M+Na]^+$: 463.0, Found: 463.0.

<u>FTIR</u> (neat): 3528, 3292, 3103, 2924, 1528, 1347, 1071, 853 cm^{-1}.

<u>HPLC</u>: (Chiralcel AD-H column, hexanes:*i*-PrOH = 93:07, 1.00 mL/min, 254 nm), *ee* =96% from 4-bromobenzyl alcohol, *ee* = 97% from 4-bromobenzaldehyde.

<u>$[\alpha]^{20}_D$ =</u> +21.25 ° (c 1.60, $CHCl_3$).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2.01
1.00
1.00
2.00
0.95
1.04
0.98
1.03
0.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
150.23
145.77
140.39
133.72
131.65
128.42
128.02
124.58
121.97
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74.13
51.08
44.35
OH
Br
NHNs
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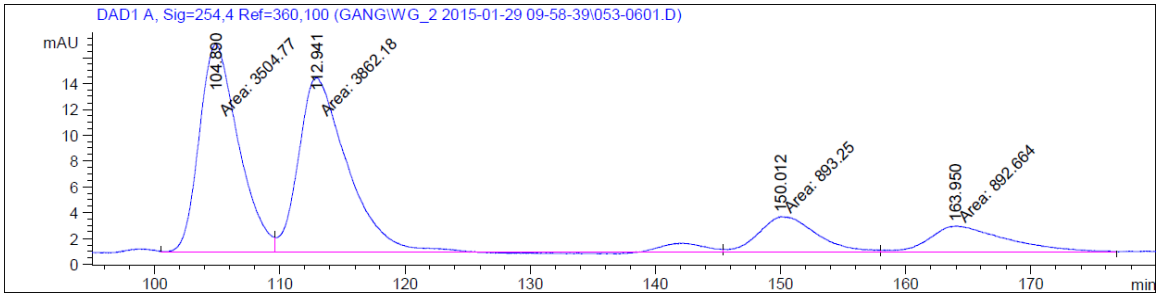
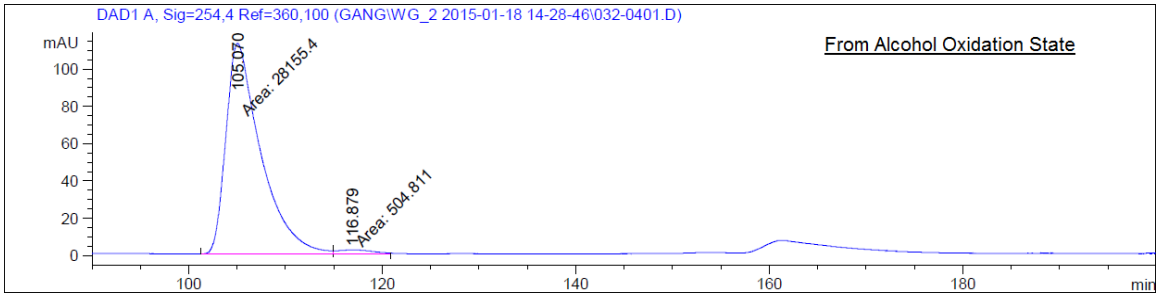
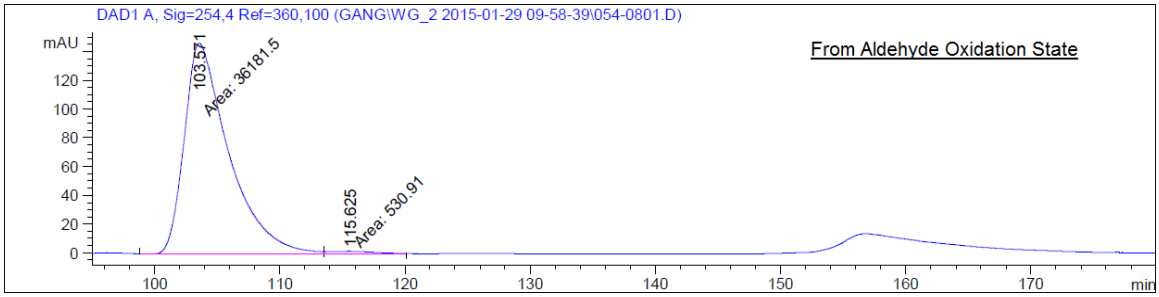


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	104.890	MF	3.6075	3504.76978	16.19220	38.2915
2	112.941	MF	4.7573	3862.17676	13.53059	42.1964
3	150.012	FM	5.3597	893.25012	2.77766	9.7592
4	163.950	FM	7.2431	892.66431	2.05405	9.7528
Totals :				9152.86096	34.55450	

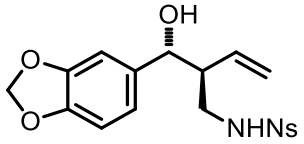


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	105.070	MF	4.1566	2.81554e4	112.89343	98.2386
2	116.879	FM	4.1547	504.81134	2.02504	1.7614
Totals :				2.86602e4	114.91847	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	103.571	MF	4.1140	3.61815e4	146.57938	98.5539
2	115.625	FM	4.4746	530.91046	1.97748	1.4461
Totals :				3.67125e4	148.55686	

***N*-((*S*)-2-((*R*)-benzo[d][1,3]dioxol -5-yl(hydroxy)methyl)but-3-en-1-yl)-4-nitrobenzensulfonamide (3.4d)**



<u>*From alcohol oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with piperonyl alcohol (15.2 mg, 0.1 mmol, 100 mol%), the product **3.4d** was obtained as gel in 73% yields (29.7 mg, 0.073 mmol, *anti:syn*=4:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). <u>*From aldehyde oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with piperonal (15.0 mg, 0.1 mmol, 100 mol%), the product **3.4d** was obtained as gel in 87% yields (35.3 mg, 0.087 mmol, *anti:syn*=4:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

<u>^{1}H NMR (400 MHz, $CDCl_3$)</u> δ 8.36 (d, *J* = 8.5 Hz, 2H), 7.98 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.67–6.58 (m, 2H), 5.94 (dd, *J* = 5.2, 1.3 Hz, 2H), 5.56 (dt, *J* = 17.4, 9.6 Hz, 1H), 5.22 (d, *J* = 10.3 Hz, 1H), 5.07 (d, *J* = 17.2 Hz, 1H), 4.60 (d, *J* = 3.7 Hz, 1H), 3.04 (dt, *J* = 12.8, 6.6 Hz, 1H), 2.92 (ddd, *J* = 12.5, 7.0, 5.4 Hz, 1H), 2.52–2.41 (m, 1H), 2.20 (s, 1H).

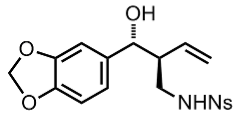
<u>^{13}C NMR (100 MHz, $CDCl_3$)</u> δ 150.2, 147.9, 147.5, 145.7, 134.9, 134.6, 128.4, 124.5, 120.7, 119.9, 108.2, 106.6, 101.3, 75.1, 51.1, 44.2.

<u>LRMS</u> (ESI) Calcd. for $C_{18}H_{18}N_2O_7SNa$ $[M+Na]^+$: 429.1, Found: 429.1.

<u>FTIR</u> (neat): 3326, 3303, 2923, 1504, 1402, 1349, 1093, 926, 853 cm^{-1}.

<u>HPLC</u>: (Chiralcel AD-H column, hexanes:*i*-PrOH = 80:20, 1.00 mL/min, 254 nm), *ee* =96% from piperonyl alcohol, *ee* = 97% from piperonal.

<u>$[\alpha]^{20}_D$ =</u> +3.92 ° (c 0.51, $CHCl_3$).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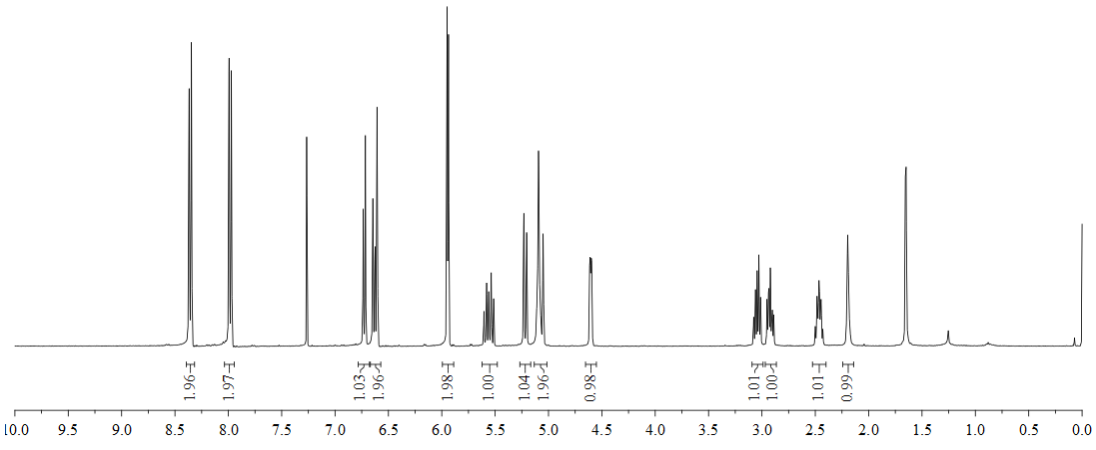
O
NHNs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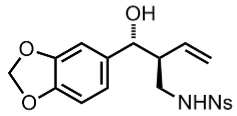
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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O
NHNs

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106.60
101.35
75.07
51.06
44.20
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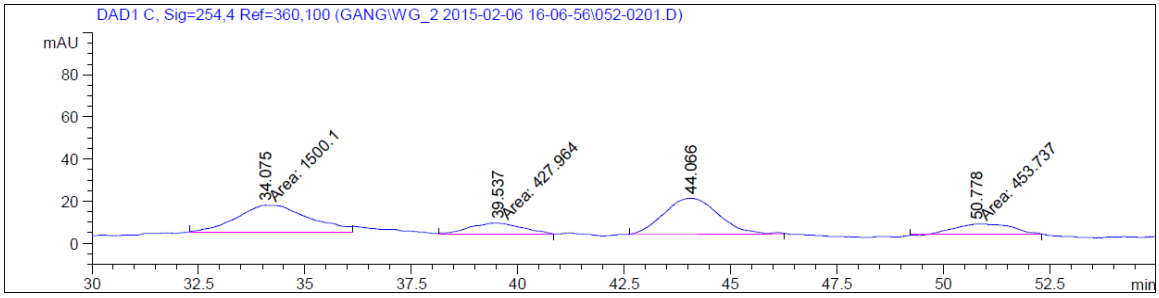
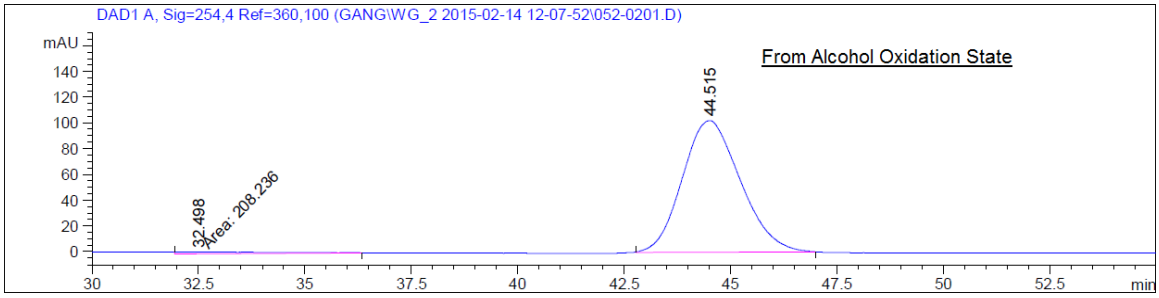
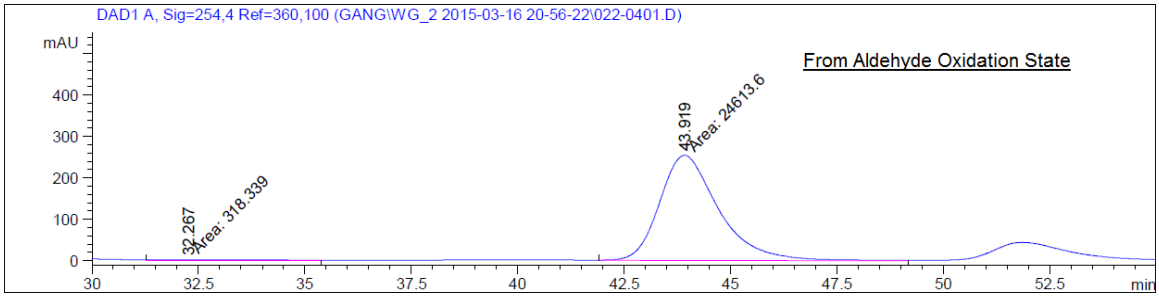


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.075	MM	1.9617	1500.10156	12.74461	38.3599
2	39.537	MM	1.4086	427.96353	5.06375	10.9437
3	44.066	BB	1.0521	1528.79712	17.01666	39.0937
4	50.778	MM	1.5574	453.73697	4.85577	11.6027
Totals :				3910.59918	39.68081	

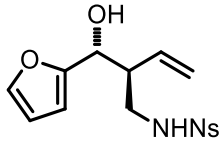


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.498	MM	2.4435	208.23582	1.42035	2.0991
2	44.515	BB	1.3732	9712.10645	102.33710	97.9009
Totals :				9920.34227	103.75745	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.267	MF	3.2955	318.33871	1.60995	1.2768
2	43.919	FM	1.6125	2.46136e4	254.40469	98.7232
Totals :				2.49320e4	256.01464	

***N*-((*S*)-2-((*R*)-furan-2-yl(hydroxy)methyl)but-3-en-1-yl)-4-nitrobenzenesulfonamide (3.4e)**



<u>*From alcohol oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with furan-2-ylmethanol (9.8 mg, 0.1 mmol, 100 mol%), the product **3.4e** was obtained as gel in 73% yields (25.7 mg, 0.073 mmol, *anti:syn*=10:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). <u>*From aldehyde oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with furan-2-carbaldehyde (9.6 mg, 0.1 mmol, 100 mol%), the product **3.4d** was obtained as gel in 85% yields (30.0 mg, 0.085 mmol, *anti:syn*=9:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

<u>^{1}H NMR (400 MHz, $CDCl_3$)</u> δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.03 (d, *J* = 9.0 Hz, 2H), 7.33 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.23 (dt, *J* = 3.3, 0.7 Hz, 1H), 5.61 (ddd, *J* = 17.2, 10.4, 8.7 Hz, 1H), 5.26–5.20 (m, 1H), 5.18–5.05 (m, 2H), 4.76 (d, *J* = 4.1 Hz, 1H), 3.25–3.15 (m, 1H), 3.06–2.96 (m, 1H), 2.72 (dt, *J* = 13.8, 6.8 Hz, 1H), 2.23 (s, 1H).

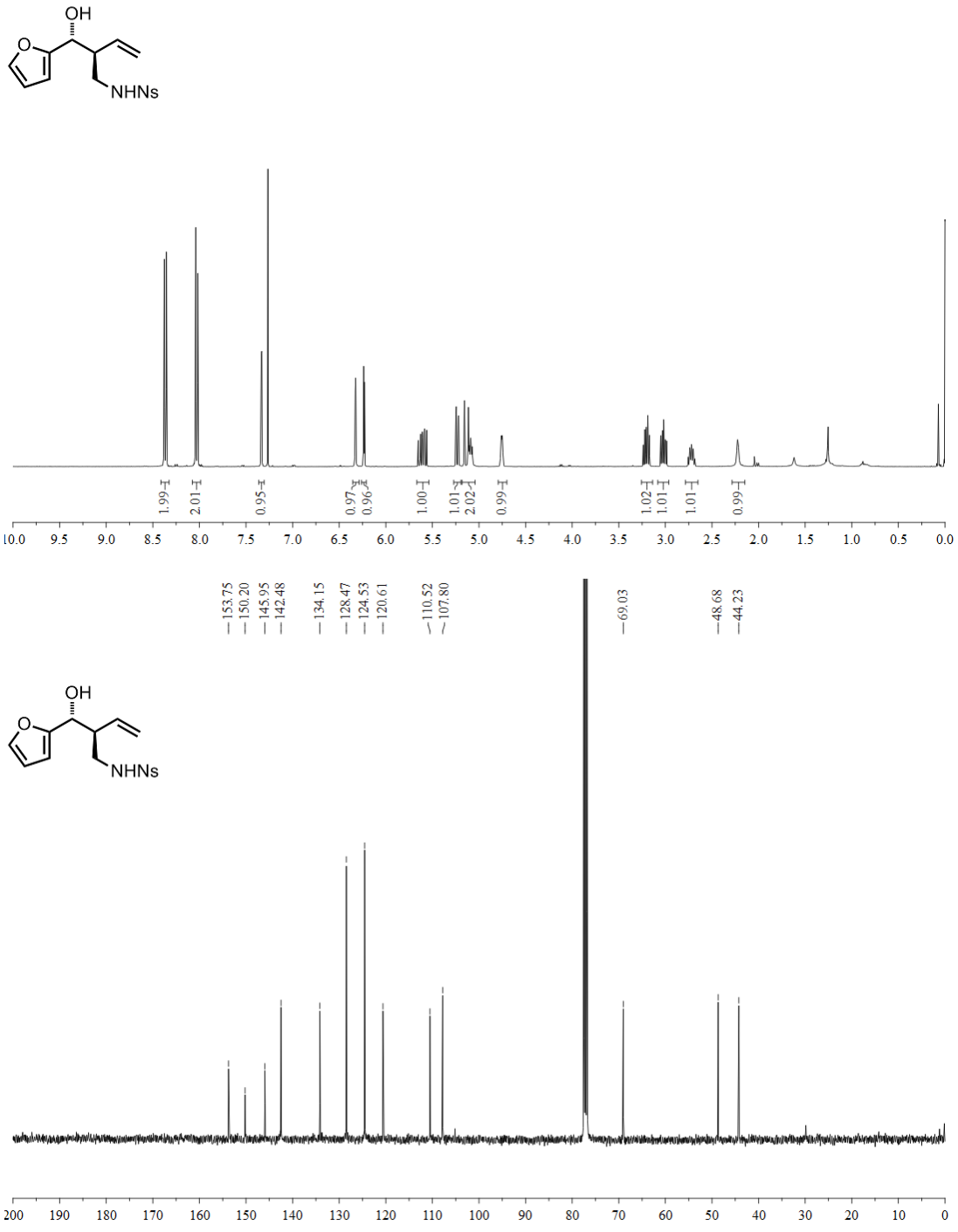
<u>^{13}C NMR (100 MHz, $CDCl_3$)</u> δ 153.8, 150.0, 145.9, 142.5, 134.2, 128.5, 124.53, 120.6, 110.5, 107.8, 69.0, 48.7, 44.2.

<u>HRMS</u> (CI) Calcd. for $C_{15}H_{16}N_2O_6SNa$ $[M+Na]^+$: 375.0621, Found: 375.0619.

<u>FTIR</u> (neat): 3295, 3107, 2925, 1528, 1402, 1348, 1093, 924, 854 cm^{-1}.

<u>HPLC</u>: (Chiralcel AD-H column, hexanes:*i*-PrOH = 87:13, 1.00 mL/min, 254 nm), *ee* =97% from furan-2-ylmethanol, *ee* = 97% from furan-2-carbaldehyde.

<u>$[\alpha]^{20}_D$ =</u> +21.00 ° (c 1.00, $CHCl_3$).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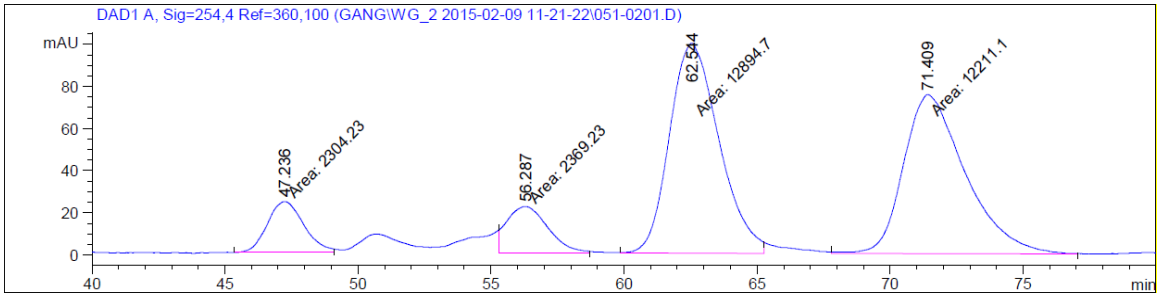
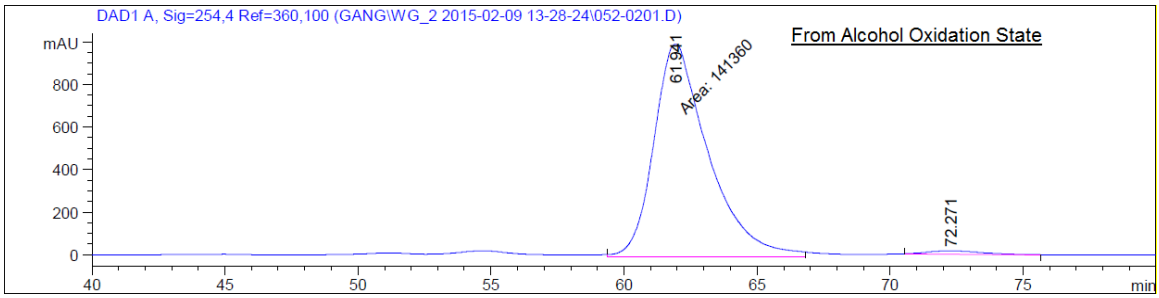
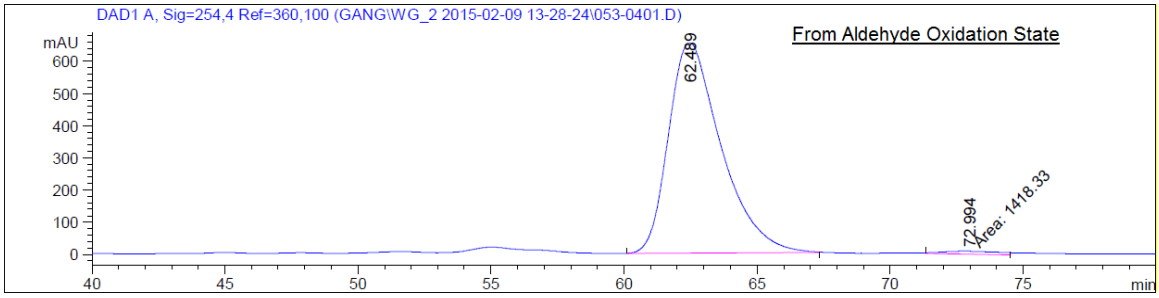


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.236	MF	1.5849	2304.23315	24.23090	7.7377
2	56.287	FM	1.7878	2369.22681	22.08704	7.9560
3	62.544	MF	2.1534	1.28947e4	99.80021	43.3008
4	71.409	FM	2.6934	1.22111e4	75.56129	41.0055
Totals :				2.97793e4	221.67943	

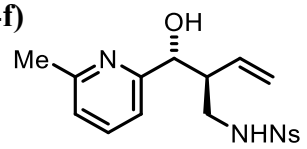


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	61.941	MM	2.3657	1.41360e5	995.89172	98.4294
2	72.271	BB	1.6968	2255.62183	15.71285	1.5706
Totals :				1.43616e5	1011.60458	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	62.489	BB	1.9525	8.97719e4	651.93475	98.4446
2	72.994	MM	2.4917	1418.33447	9.48692	1.5554
Totals :				9.11903e4	661.42168	

***N*-((*S*)-2-((*R*)-hydroxy(6-methylpyridin-2-yl)methyl)but-3-en-1-yl)-4-nitrobenzenesulfonamide (3.4f)**



<u>*From alcohol oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with (6-methylpyridin-2-yl)methanol (12.3 mg, 0.1 mmol, 100 mol%), the product **3.4f** was obtained as white solid in 78% yields (29.4 mg, 0.078 mmol, *anti:syn*=5:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-2:1). <u>*From aldehyde oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with 6-methylpicolinaldehyde (12.1 mg, 0.1 mmol, 100 mol%), the product **3.4f** was obtained as white solid in 72% yields (27.2 mg, 0.072 mmol, *anti:syn*=4:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-2:1). Spectral data is reported for the major isomer.

<u>^{1}H NMR (400 MHz, $CDCl_3$)</u> δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.07 (d, *J* = 9.0 Hz, 2H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 5.68–5.61 (m, 1H), 5.52 (ddd, *J* = 17.3, 10.4, 8.8 Hz, 1H), 4.97 (dd, *J* = 10.4, 1.5 Hz, 2H), 4.88 (ddd, *J* = 17.3, 1.5, 0.9 Hz, 1H), 4.82 (d, *J* = 3.2 Hz, 1H), 3.44–3.32 (m, 1H), 3.18 (ddd, *J* = 12.6, 6.4, 3.6 Hz, 1H), 2.68 (dtd, *J* = 9.3, 6.3, 3.3 Hz, 1H), 2.52 (s, 3H).

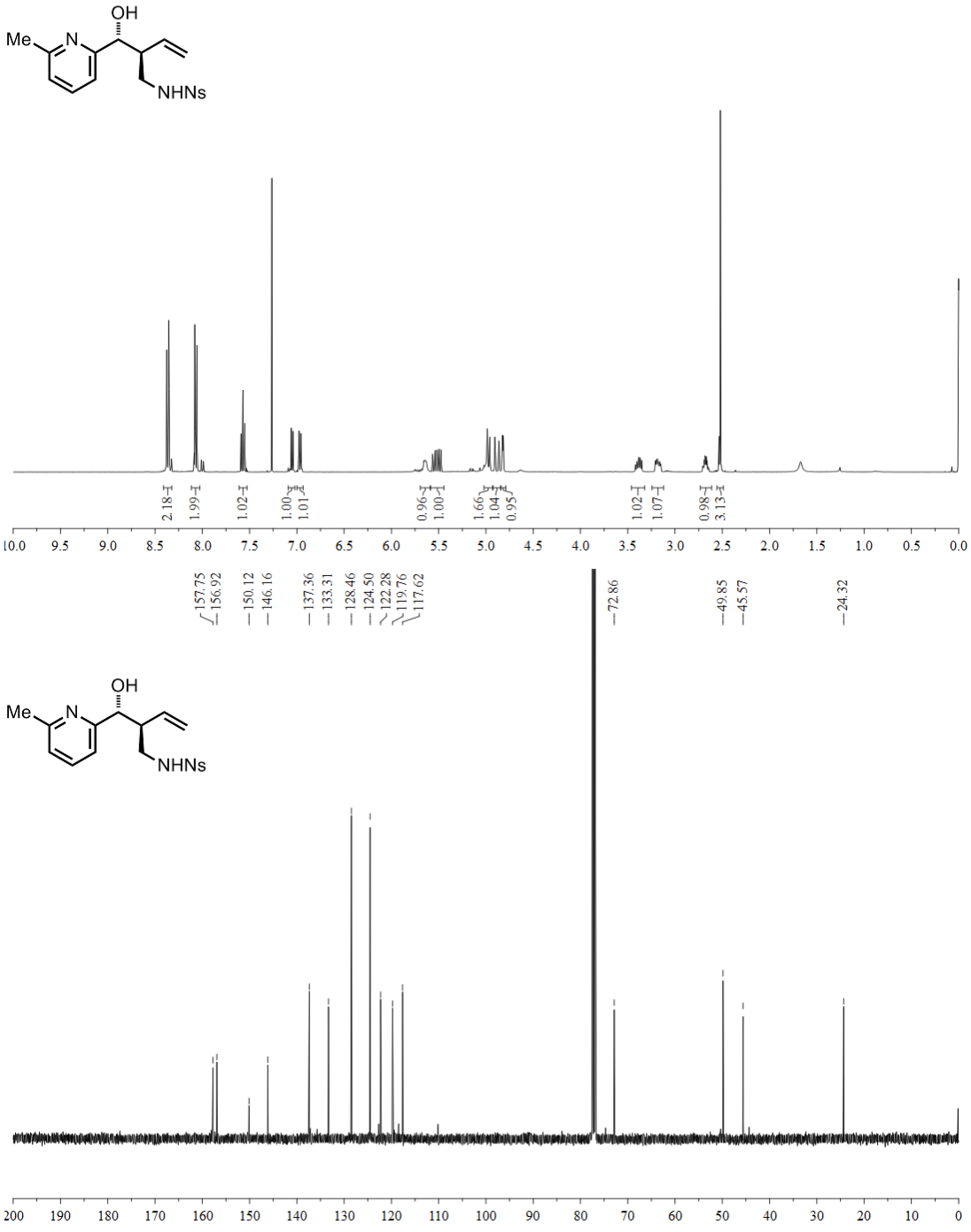
<u>^{13}C NMR (100 MHz, $CDCl_3$)</u> δ 157.8, 156.9, 150.1, 146.2, 137.4, 133.3, 128.5, 124.5, 122.3, 119.8, 117.6, 72.9, 49.9, 45.6, 24.3.

<u>HRMS</u> (CI) Calcd. for $C_{17}H_{19}N_3O_5SNa$ $[M+Na]^+$: 400.0938, Found: 400.0938.

<u>FTIR</u> (neat): 3295, 3105, 2924, 1596, 1349, 1311, 1162, 1091, 997, 928, 855 cm^{-1}.

<u>HPLC</u>: (Chiralcel AD-H column, hexanes:*i*-PrOH = 96:4, 1.00 mL/min, 254 nm), *ee* =97% from (6-methylpyridin-2-yl)methanol, *ee* = 96% from 6-methylpicolinaldehyde.

<u>$[\alpha]^{20}_D$ =</u> +22.00 ° (c 0.50, $CHCl_3$). **<u>mp:</u>** 112-115 ºC.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1.07
0.98
3.13
157.75
156.92
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137.36
133.31
128.46
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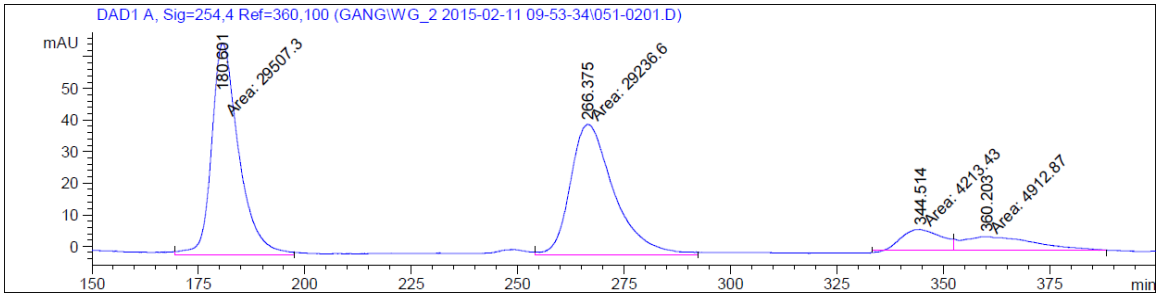
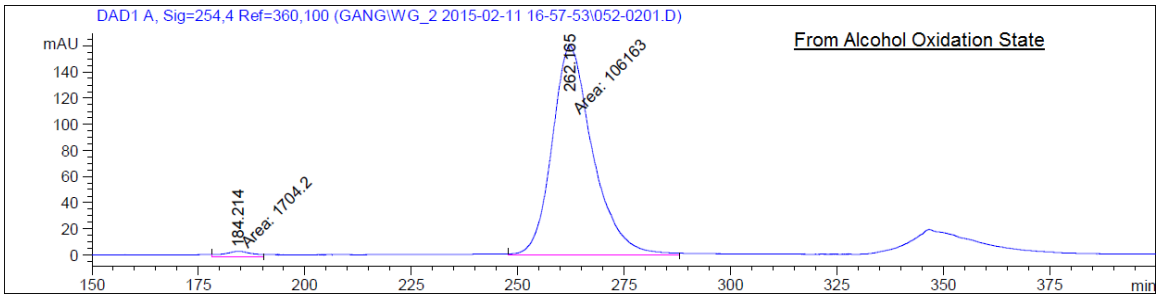
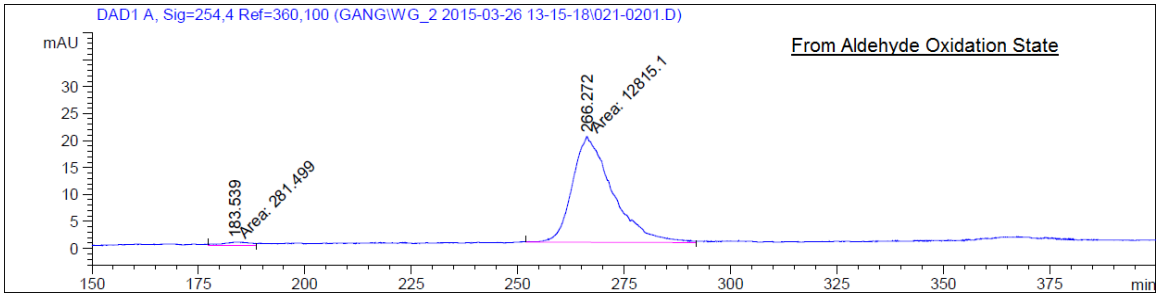
122.28
119.76
117.62
72.86
49.85
45.57
24.32



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	180.601	MF	7.3540	2.95073e4	66.87398	43.4761
2	266.375	FM	11.8185	2.92366e4	41.22987	43.0772
3	344.514	MF	10.8166	4213.42627	6.49219	6.2081
4	360.203	FM	19.2579	4912.86719	4.25182	7.2386
Totals :				6.78702e4	118.84786	

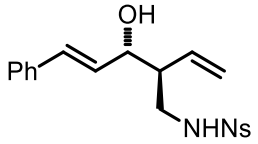


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	184.214	MM	7.6326	1704.19995	3.72133	1.5799
2	262.165	FM	10.9739	1.06163e5	161.23618	98.4201
Totals :				1.07867e5	164.95750	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	183.539	MM	7.3375	281.49930	6.39408e-1	2.1494
2	266.272	MM	10.8999	1.28151e4	19.59501	97.8506
Totals :				1.30966e4	20.23441	

***N*-((2*S*,3*S*,*E*)-3-hydroxy-5-phenyl-2-vinylpent-4-en-1-yl)-4-nitrobenzenesulfonamide (3.4g)**



<u>*From alcohol oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with cinnamyl alcohol (13.4 mg, 0.1 mmol, 100 mol%), the product **3.4g** was obtained as gel in 73% yields (28.4 mg, 0.073 mmol, *anti:syn*=6:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). <u>*From aldehyde oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with cinnamaldehyde (13.2 mg, 0.1 mmol, 100 mol%), the product **3.4g** was obtained as gel in 77% yields (30.0 mg, 0.077 mmol, *anti:syn*=5:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

<u>^{1}H NMR (400 MHz, $CDCl_3$)</u> δ 8.30 (d, *J* = 9.0 Hz, 2H), 8.02 (d, *J* = 9.0 Hz, 2H), 7.34–7.22 (m, 5H), 6.53 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.10 (dd, *J* = 15.9, 6.7 Hz, 1H), 5.67 (ddd, *J* = 17.3, 10.4, 8.6 Hz, 1H), 5.33–5.11 (m, 3H), 4.43–4.36 (m, 1H), 3.29–3.19 (m, 1H), 3.09 (m, 1H), 2.56–2.47 (m, 1H), 2.00 (d, *J* = 3.5 Hz, 1H).

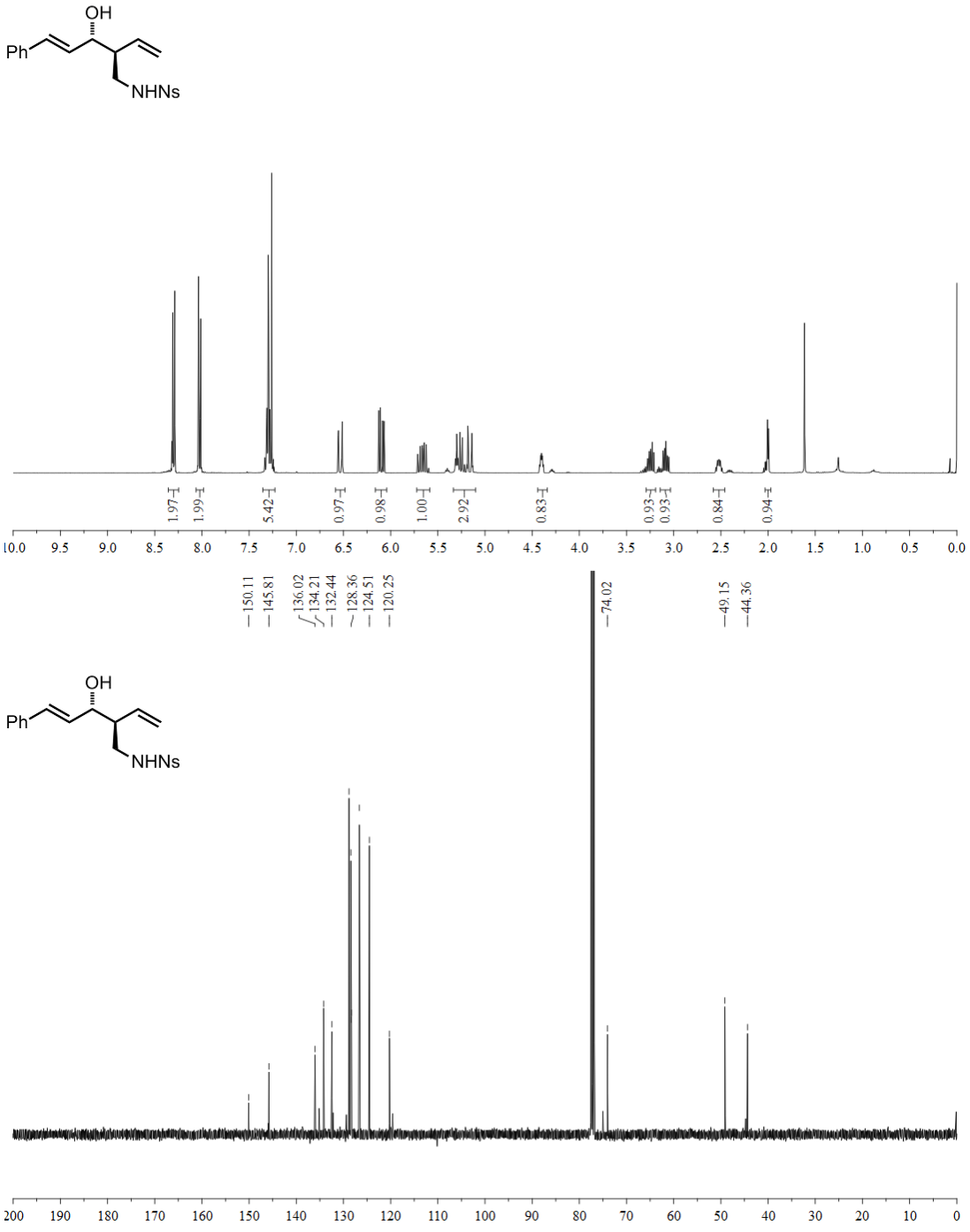
<u>^{13}C NMR (100 MHz, $CDCl_3$)</u> δ 150.1, 145.8, 136.0, 134.2, 132.4, 128.8, 128.4, 128.4, 128.3, 126.6, 124.5, 120.3, 74.0, 49.2, 44.4.

<u>LRMS</u> (ESI) Calcd. for $C_{19}H_{20}N_2O_5SNa$ $[M+Na]^+$: 411.1, Found: 411.1.

<u>FTIR</u> (neat): 3325, 3302, 2919, 1529, 1348, 1311, 1163, 1093, 853 cm^{-1}.

<u>HPLC</u>: (Chiralcel AD-H column, hexanes:*i*-PrOH = 80:20, 1.00 mL/min, 254 nm), *ee* =95% from connamyl alcohol, *ee* = 98% from cinnamaldehyde.

<u>$[\alpha]^{20}_D$ =</u> -9.00 ° (c 1.00, $CHCl_3$).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1.00
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0.83
0.93
0.93
0.84
0.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
150.11
145.81
136.02
134.21
132.44
128.36
124.51
120.25
74.02
49.15
44.36
OH
Ph
NHNs
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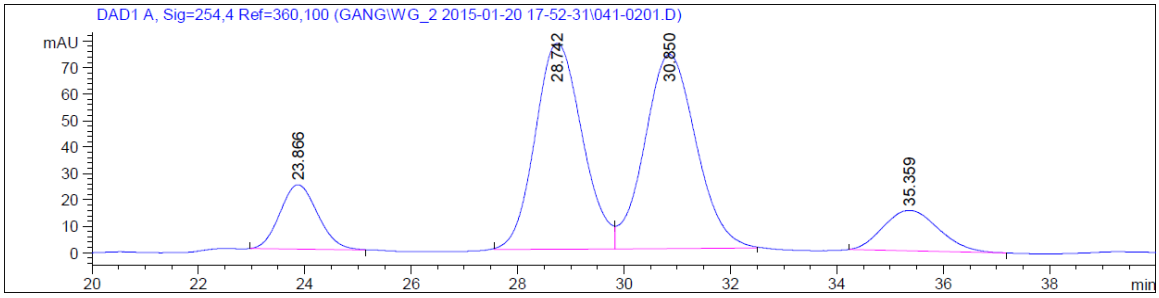
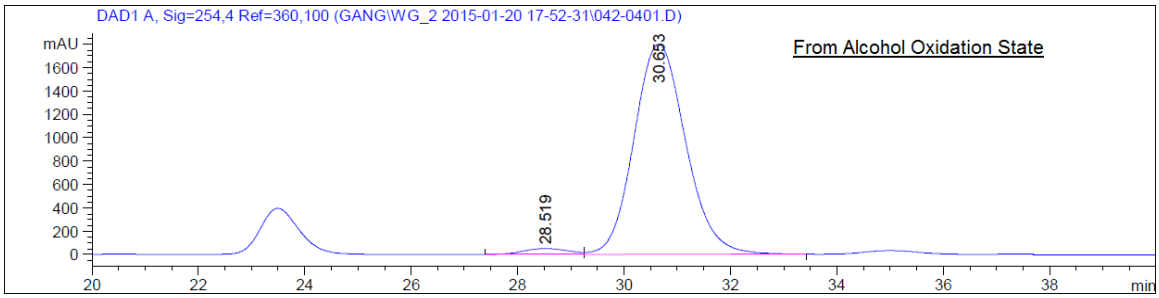
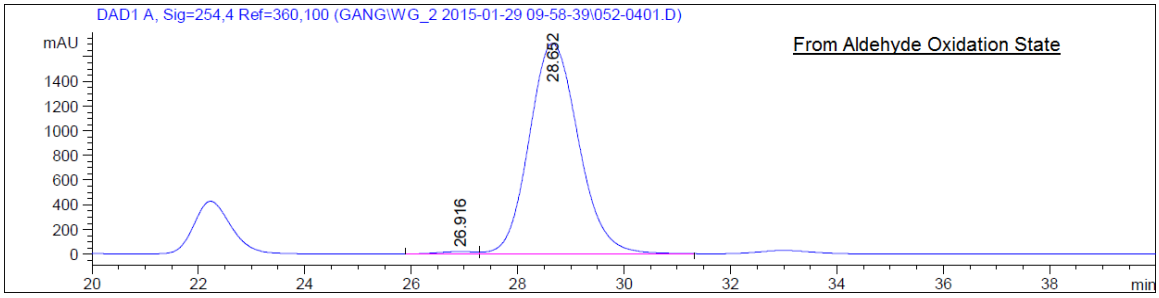


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.866	BB	0.7397	1200.67273	24.41639	9.9708
2	28.742	BV	0.9451	4800.95166	77.89568	39.8688
3	30.850	VB	1.0109	4929.60107	73.45772	40.9371
4	35.359	BB	0.8600	1110.65454	15.31675	9.2233
Totals :				1.20419e4	191.08655	

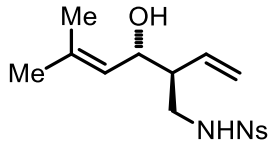


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.519	BV	0.8819	2941.61499	50.77702	2.3672
2	30.653	VB	1.0520	1.21322e5	1796.11804	97.6328
Totals :				1.24263e5	1846.89506	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.916	BV	0.6950	927.20190	19.42047	0.8394
2	28.652	VB	1.0031	1.09536e5	1705.98291	99.1606
Totals :				1.10463e5	1725.40338	

***N*-((2*S*,3*S*)-3-hydroxy-5-methyl-2-vinylhex-4-en-1-yl)-4-nitrobenzenesulfonamide (3.4h)**



<u>*From alcohol oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with prenol (8.6 mg, 0.1 mmol, 100 mol%), the product **3.4h** was obtained as gel in 70% yields (23.8 mg, 0.070 mmol, *anti:syn*=8:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). <u>*From aldehyde oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with prenal (8.4 mg, 0.1 mmol, 100 mol%), the product **3.4h** was obtained as gel in 96% yields (32.6 mg, 0.096 mmol, *anti:syn*=7:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

<u>^{1}H NMR (400 MHz, $CDCl_3$)</u> δ 8.38 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 9.0 Hz, 2H), 5.59 (ddd, *J* = 17.2, 10.3, 9.1 Hz, 1H), 5.23 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.2 –5.08 (m, 3H), 4.42–4.33 (m, 1H), 3.25 (dt, *J* = 12.8, 6.6 Hz, 1H), 2.97 (ddd, *J* = 12.4, 7.6, 4.7 Hz, 1H), 2.30 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.72 (d, *J* = 1.3 Hz, 3H), 1.65 (d, *J* = 1.3 Hz, 3H), 1.52 (d, *J* = 2.8 Hz, 1H).

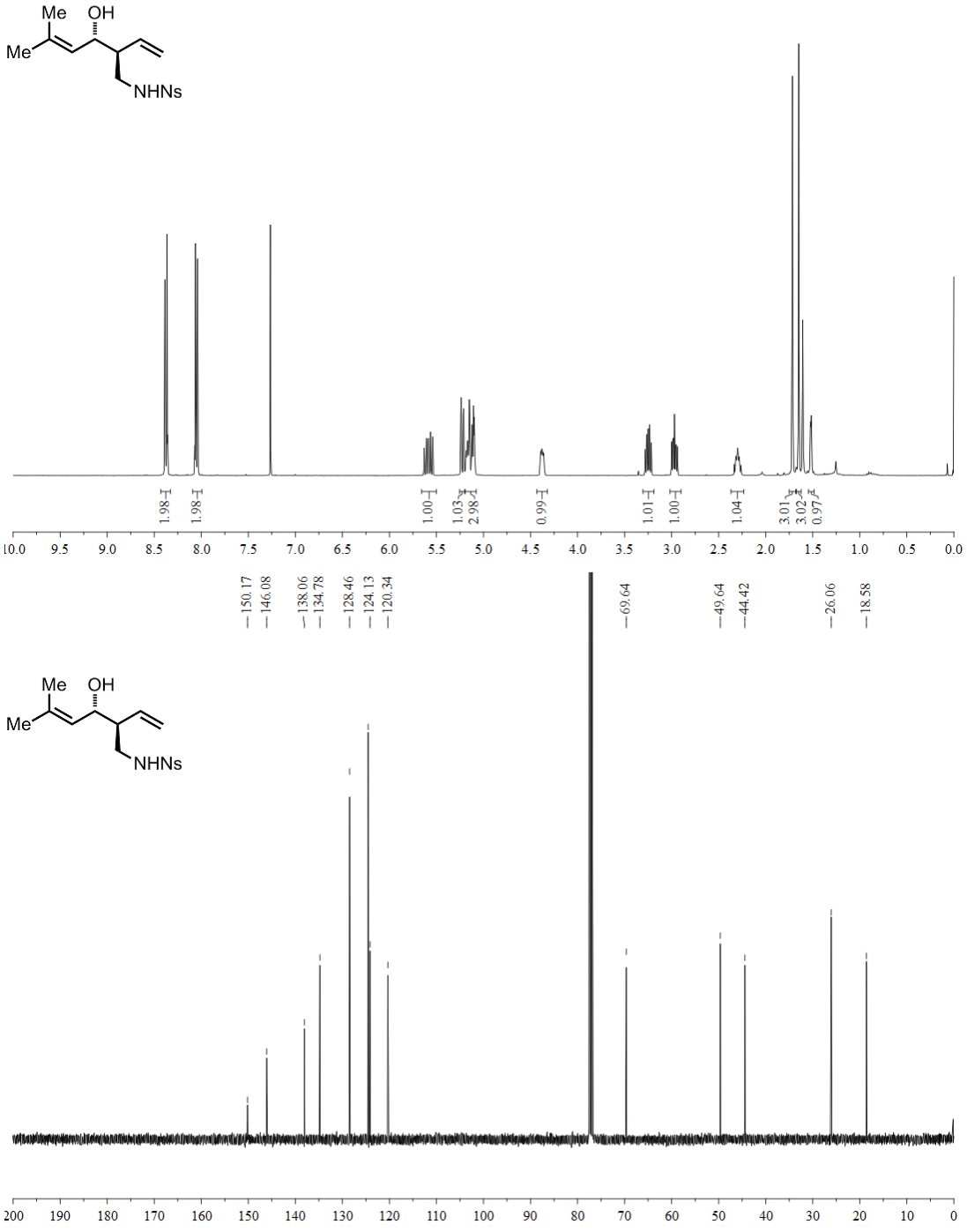
<u>^{13}C NMR (100 MHz, $CDCl_3$)</u> δ 150.2, 146.1, 138.1, 134.8, 128.5, 124.5, 124.1, 120.3, 69.6, 49.6, 44.4, 26.1, 18.6.

<u>LRMS</u> (ESI) Calcd. for $C_{15}H_{20}N_2O_5SNa$ $[M+Na]^+$: 363.1, Found: 363.1.

<u>FTIR</u> (neat): 2922, 2852, 1530, 1349, 1309, 1163,1093, 926, 853 cm^{-1}.

<u>HPLC</u>: (Chiralcel AD-H column, hexanes:*i*-PrOH = 93:07, 1.00 mL/min, 254 nm), *ee* =95% from prenol, *ee* = 99% from prenal.

<u>$[\alpha]^{20}_D$ =</u> -43.30 ° (c 0.50, $CHCl_3$).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1.00
1.03
2.98
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1.01
1.00
1.04
3.01
3.02
0.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
150.17
146.08
138.06
134.78
128.46
124.13
120.34
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49.64
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Me
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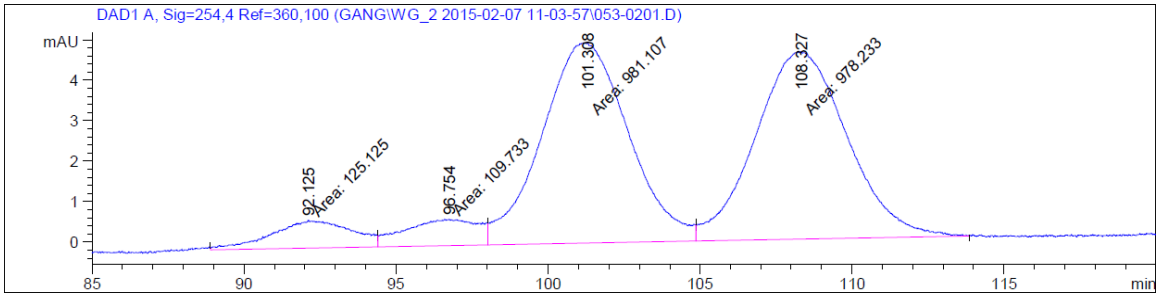
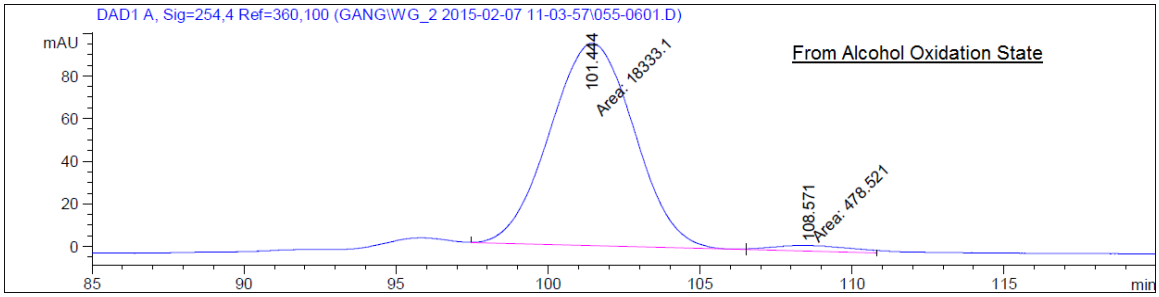
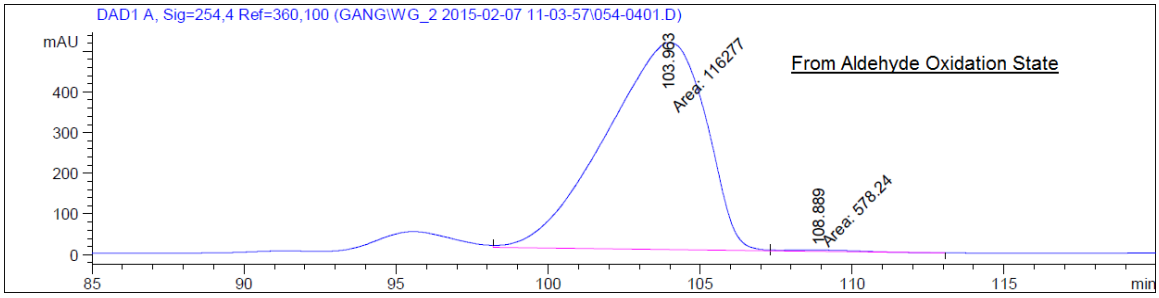


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	92.125	MF	3.0125	125.12487	6.92250e-1	5.7025
2	96.754	FM	2.8216	109.73318	6.48185e-1	5.0011
3	101.308	FM	3.2983	981.10657	4.95763	44.7137
4	108.327	FM	3.5125	978.23309	4.64167	44.5827
Totals :				2194.19772	10.93974	

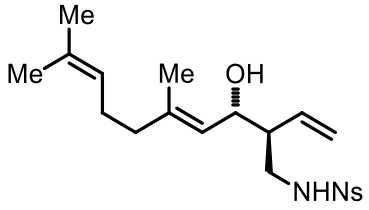


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	101.444	MF	3.2148	1.83331e4	95.04454	97.4563
2	108.571	FM	3.0220	478.52057	2.63910	2.5437
Totals :				1.88116e4	97.68364	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	103.963	MF	3.8072	1.16277e5	509.02383	99.5052
2	108.889	FM	2.6513	578.23993	3.63501	0.4948
Totals :				1.16856e5	512.65884	

***N*-((2*S*,3*S*,*E*)-3-hydroxy-5,9-dimethyl-2-vinyldeca-4,8-dien-1-yl)-4-nitrobenzenesulfonamide (3.4i)**



<u>*From alcohol oxidation level:*</u> According to general procedure (reaction time was 48 h) for coupling of vinyl aziridine (**3.3a**) with greniol (15.4 mg, 0.1 mmol, 100 mol%), the product **3.4i** was obtained as gel in 67% yields (27.3 mg, 0.067 mmol, *anti:syn*=9:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). <u>*From aldehyde oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with (*E*)-citral (15.2 mg, 0.1 mmol, 100 mol%), the product **3.4i** was obtained as gel in 66% yields (27.0 mg, 0.066 mmol, *anti:syn*=8:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

<u>^{1}H NMR (400 MHz, $CDCl_3$)</u> δ 8.37 (d, *J* = 8.9 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 5.57 (ddd, *J* = 17.2, 10.3, 9.1 Hz, 1H), 5.25–5.18 (m, 2H), 5.16–4.98 (m, 3H), 4.41 (dd, *J* = 9.0, 4.6 Hz, 1H), 3.25 (dt, *J* = 12.9, 6.6 Hz, 1H), 2.98 (ddd, *J* = 12.4, 7.4, 4.8 Hz, 1H), 2.31 (dt, *J* = 13.6, 6.9 Hz, 1H), 2.10–1.95 (m, 4H), 1.70–1.56 (m, 9H), 1.52 (brs, 1H).

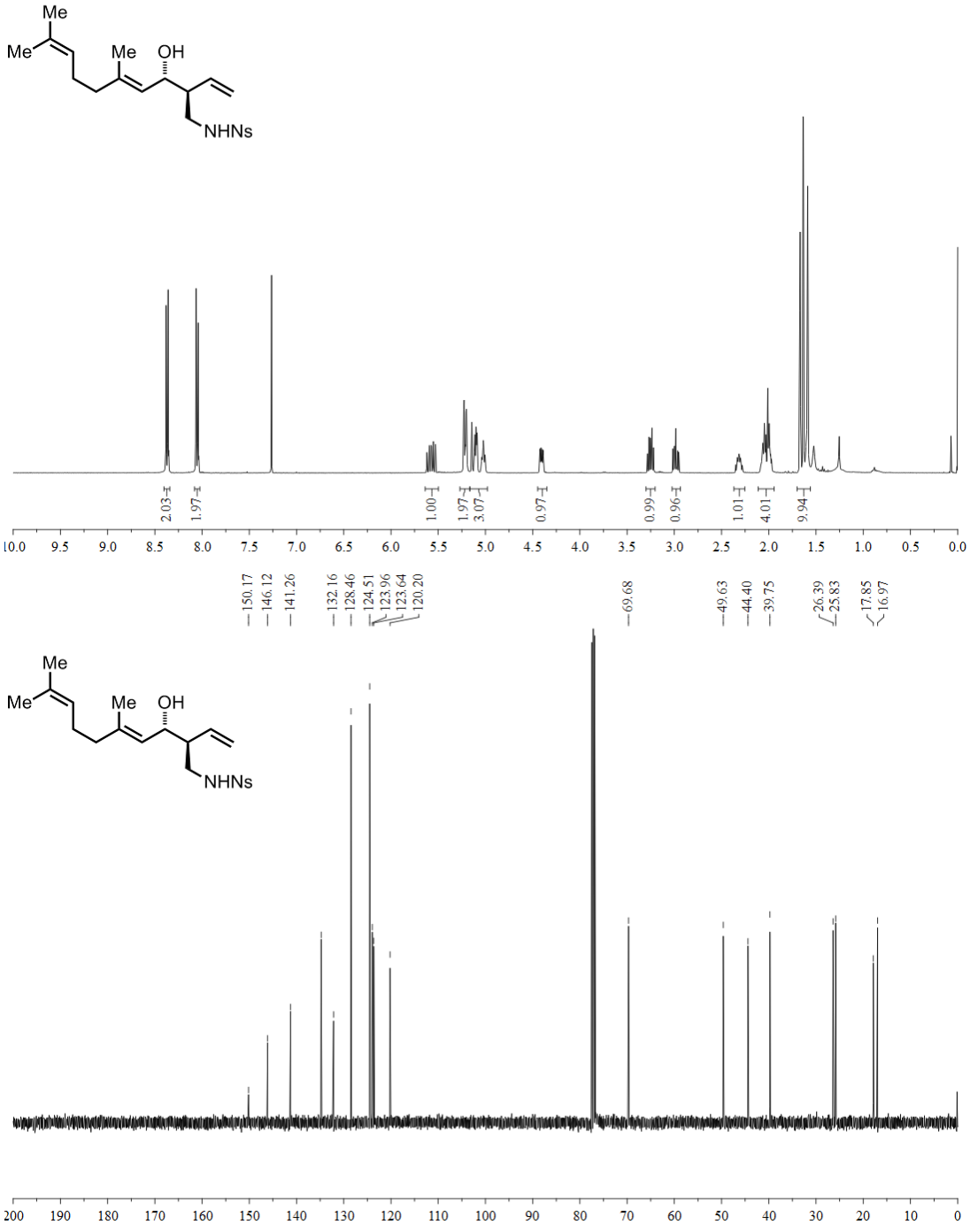
<u>^{13}C NMR (100 MHz, $CDCl_3$)</u> δ 150.2, 146.1, 141.3, 134.8, 132.2, 128.5, 124.5, 123.9, 123.6, 120.2, 69.7, 49.6, 44.4, 39.8, 26.4, 25.8, 17.9, 17.0.

<u>LRMS</u> (ESI) Calcd. for $C_{20}H_{28}N_2O_5SNa$ $[M+Na]^+$: 431.2, Found: 431.2.

<u>FTIR</u> (neat): 2967, 2922, 1530, 1437, 1349, 1310, 1164, 1093, 998, 923, 854 cm^{-1}.

<u>HPLC</u>: (Chiralcel AD-H column, hexanes:*i*-PrOH = 80:20, 1.00 mL/min, 254 nm), *ee* =94% from greniol, *ee* = 91% from (*E*)-citral.

<u>$[\alpha]^{20}_D$ =</u>-14.00 ° (c 1.00, $CHCl_3$).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4.01
9.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
150.17
146.12
141.26
132.16
128.46
124.51
123.96
123.64
120.20
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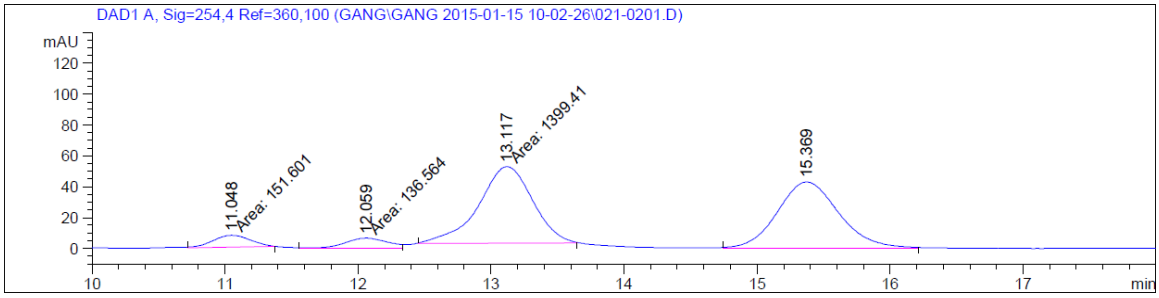
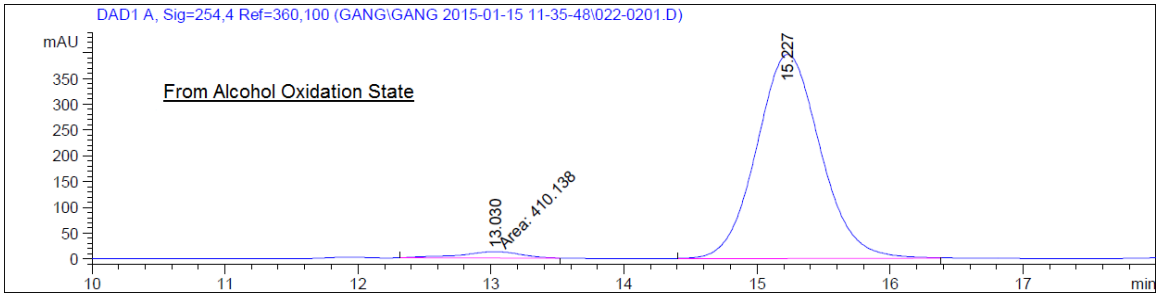
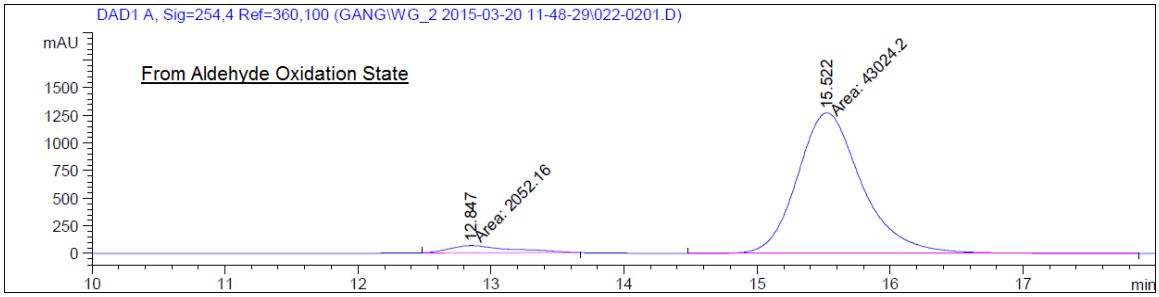


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.048	MM	0.3275	151.60112	7.71468	4.9654
2	12.059	MM	0.3622	136.56447	6.28369	4.4729
3	13.117	MM	0.4713	1399.40588	49.48650	45.8347
4	15.369	BB	0.4889	1365.58447	42.72807	44.7270
Totals :				3053.15594	106.21294	

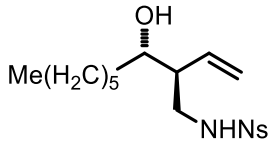


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.030	MM	0.5418	410.13779	12.61557	3.0171
2	15.227	BB	0.5144	1.31839e4	396.05563	96.9829
Totals :				1.35940e4	408.67120	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.847	MM	0.5251	2137.13159	67.83609	4.7569
2	15.522	MM	0.5600	4.27900e4	1273.57959	95.2431
Totals :				4.49271e4	1341.41568	

***N*-((2*S*,3*S*)-3-hydroxy-2-vinylnonyl)-4-nitrobenzenesulfonamide (3.4j)**



From alcohol oxidation level: According to general procedure for coupling of vinyl aziridine (**3.3a**) with 1-heptanol (11.6 mg, 0.1 mmol, 100 mol%), the product **3.4j** was obtained as gel in 96% yields (35.5 mg, 0.096 mmol, *anti:syn*=6:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). *From aldehyde oxidation level:* According to general procedure for coupling of vinyl aziridine (**3.3a**) with heptanal (11.4 mg, 0.1 mmol, 100 mol%), the product **3.4j** was obtained as gel in 90% yields (33.3 mg, 0.090 mmol, *anti:syn*=5:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 9.0 Hz, 2H), 5.65 (ddd, *J* = 17.3, 10.4, 9.0 Hz, 1H), 5.22 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.16 (dd, *J* = 7.1, 4.5 Hz, 1H), 5.11 (ddd, *J* = 17.3, 1.5, 0.8 Hz, 1H), 3.68 (t, *J* = 6.0 Hz, 1H), 3.25 (ddd, *J* = 12.6, 7.5, 6.7 Hz, 1H), 3.04 (ddd, *J* = 12.5, 7.1, 4.3 Hz, 1H), 2.28 (qd, *J* = 6.9, 3.0 Hz, 1H), 1.44–1.15 (m, 11H), 0.87 (t, *J* = 6.9 Hz, 3H).

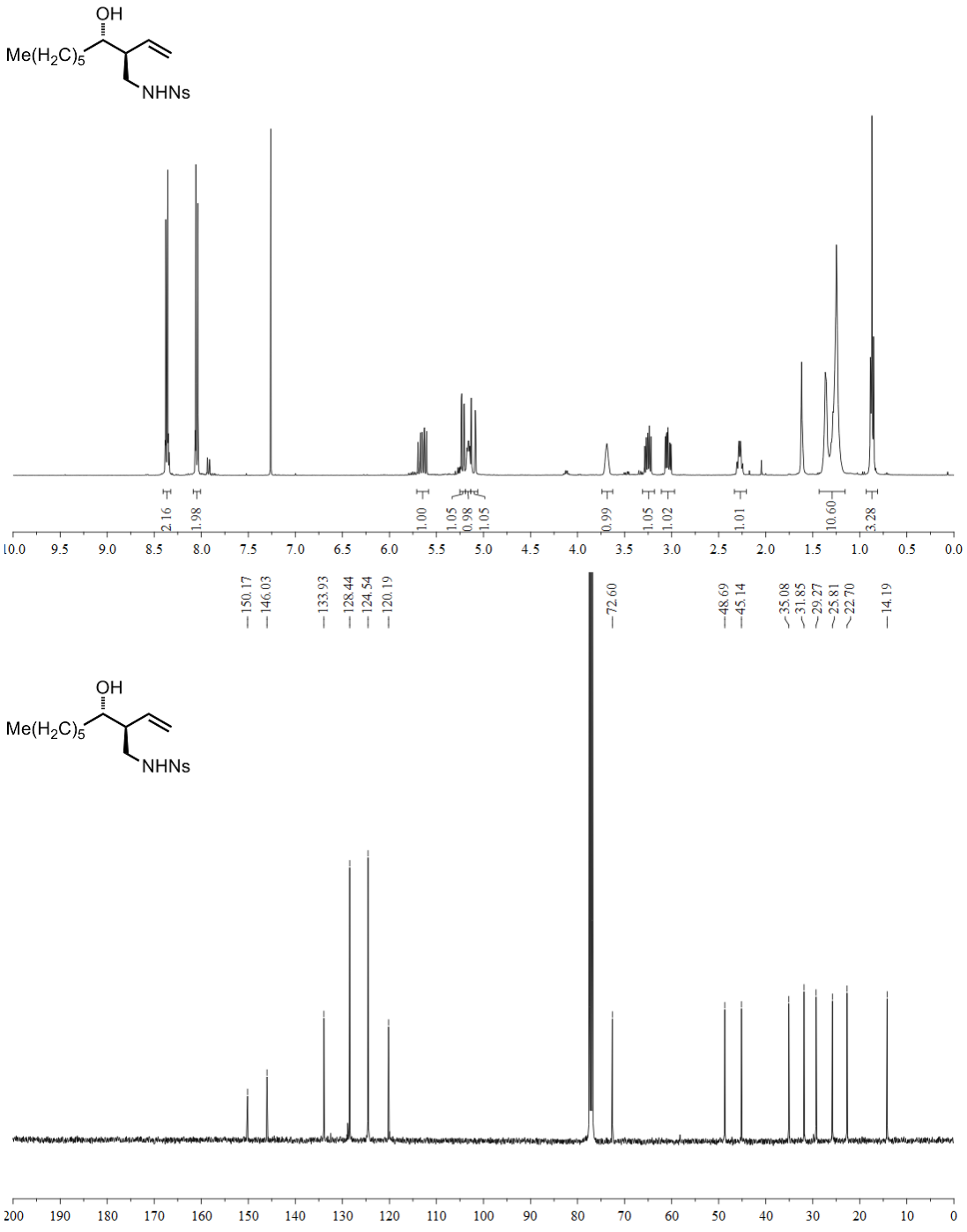
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 146.0, 133.9, 128.4, 124.5, 120.2, 72.6, 48.7, 45.1, 35.1, 31.9, 29.3, 25.8, 22.7, 14.2.

HRMS (CI) Calcd. for $C_{17}H_{26}N_2O_5SNa$ $[M+Na]^+$: 393.1455, Found: 393.1456.

FTIR (neat): 3287, 2945, 2925, 1530, 1420, 1347, 1312, 1093, 1006, 935, 855 cm^{-1}.

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 87:13, 1.00 mL/min, 254 nm), *ee* =99% from 1-heptanol, *ee* = 96% from heptanal.

$[\alpha]^{20}_D$ = +2.00 ° (c 1.00, $CHCl_3$).


OH
Me(H2C)5
NHNs
2.16
1.98
1.00
1.05
0.98
1.05
0.99
1.05
1.02
1.01
10.60
3.28
150.17
146.03
133.93
128.44
124.54
120.19
72.60
48.69
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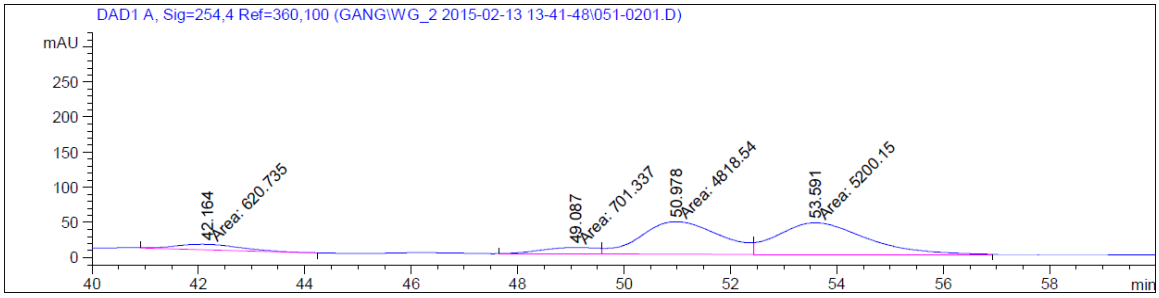
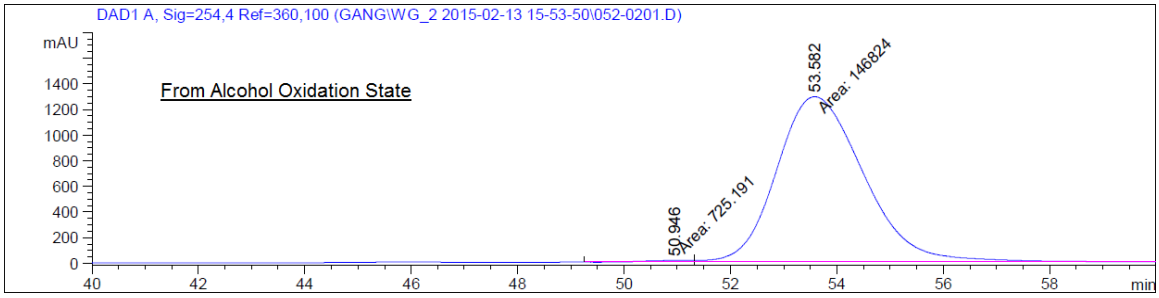
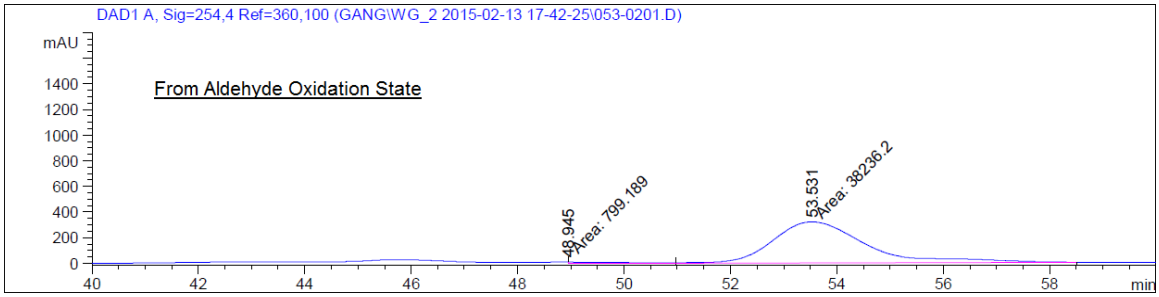
35.08
31.85
29.27
25.81
22.70
14.19



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.164	MM	1.3645	620.73486	7.58185	5.4735
2	49.087	MF	1.2277	701.33722	9.52073	6.1842
3	50.978	MF	1.7350	4818.54102	46.28659	42.4887
4	53.591	FM	1.9347	5200.14648	44.79723	45.8536
Totals :				1.13408e4	108.18639	

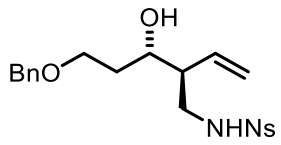


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.946	MF	1.0149	725.19067	11.90958	0.4915
2	53.582	FM	1.8945	1.46824e5	1291.68787	99.5085
Totals :				1.47550e5	1303.59745	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.945	MF	1.2590	799.18939	10.57998	2.0473
2	53.531	FM	1.9927	3.82362e4	319.79437	97.9527
Totals :				3.90354e4	330.37435	

***N*-((2*S*,3*S*)-5-(benzyloxy)-3-hydroxy-2-vinylpentyl)-4-nitrobenzenesulfonamide (3.4k)**



From alcohol oxidation level: According to general procedure for coupling of vinyl aziridine (**3.3a**) with 3-(benzyloxy)propan-1-ol (16.6 mg, 0.1 mmol, 100 mol%), the product **3.4k** was obtained as gel in 87% yields (36.5 mg, 0.087 mmol, *anti:syn*=8:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). *From aldehyde oxidation level:* According to general procedure for coupling of vinyl aziridine (**3.3a**) with 3-(benzyloxy)propanal (16.4 mg, 0.1 mmol, 100 mol%), the product **3.4k** was obtained as gel in 85% yields (35.7 mg, 0.085 mmol, *anti:syn*=7:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 9.0 Hz, 2H), 8.03 (d, *J* = 9.0 Hz, 2H), 7.40–7.27 (m, 5H), 5.69 (ddd, *J* = 17.3, 10.4, 8.9 Hz, 1H), 5.56–5.47 (m, 1H), 5.17 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.07 (ddd, *J* = 17.3, 1.5, 0.9 Hz, 1H), 4.50 (s, 2H), 3.96 (d, *J* = 10.2 Hz, 1H), 3.72 (dt, *J* = 8.6, 4.2 Hz, 1H), 3.62 (td, *J* = 9.7, 3.1 Hz, 1H), 3.47 (brs, 1H), 3.27–3.17 (m, 1H), 3.08 (ddd, *J* = 12.4, 6.3, 4.7 Hz, 1H), 2.28 (qd, *J* = 6.7, 2.9 Hz, 1H), 1.76 (dtd, *J* = 14.4, 10.2, 4.2 Hz, 1H), 1.55–1.45 (m, 1H).

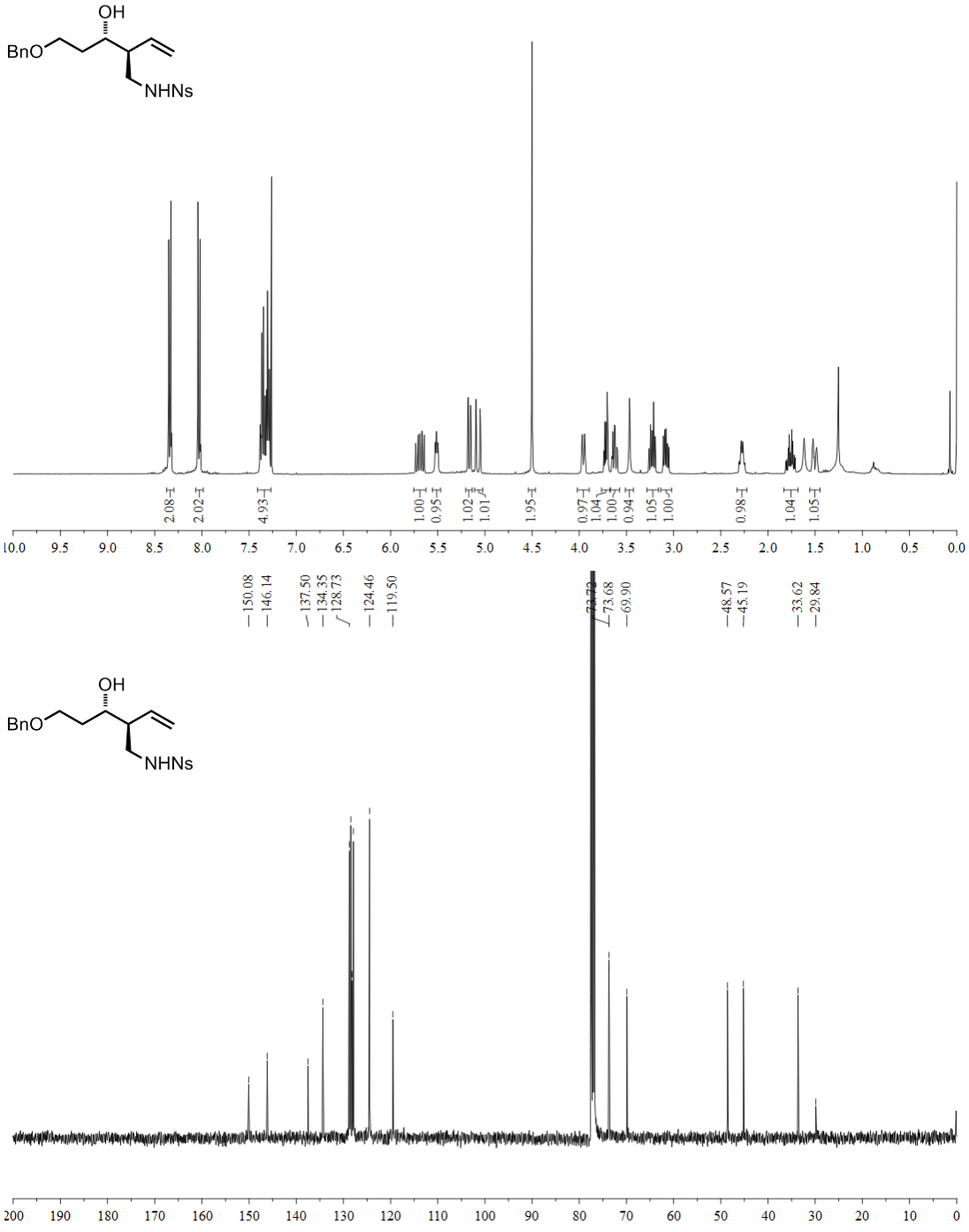
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 146.1, 137.5, 134.4, 128.7, 128.4, 128.2, 127.9, 124.5, 119.5, 73.7, 73.7, 69.9, 48.6, 45.2, 33.6, 29.8.

LRMS (ESI) Calcd. for $C_{20}H_{24}N_2O_6SNa$ $[M+Na]^+$: 443.1, Found: 443.1.

FTIR (neat): 3297, 2923, 2861, 1738, 1529, 1348, 1162, 1091, 1006, 926, 854 cm^{-1}.

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 87:13, 1.00 mL/min, 254 nm), *ee* =98% from 3-(benzyloxy)propan-1-ol, *ee* = 95% from 3-(benzyloxy)propanal.

$[\alpha]^{20}_D$ = +8.76 ° (c 1.15, $CHCl_3$).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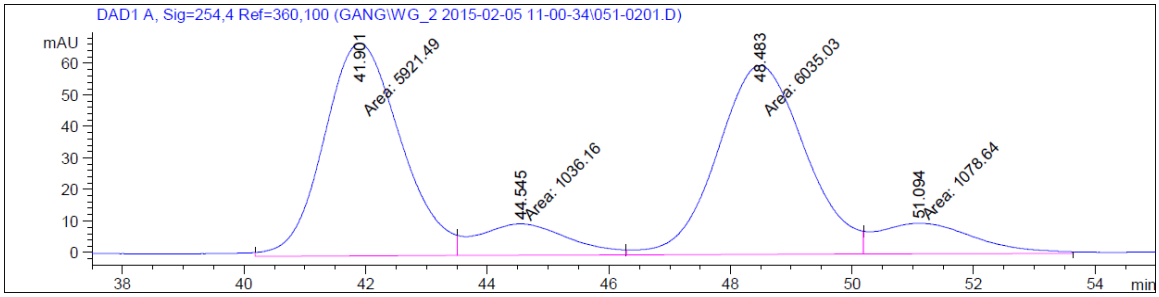
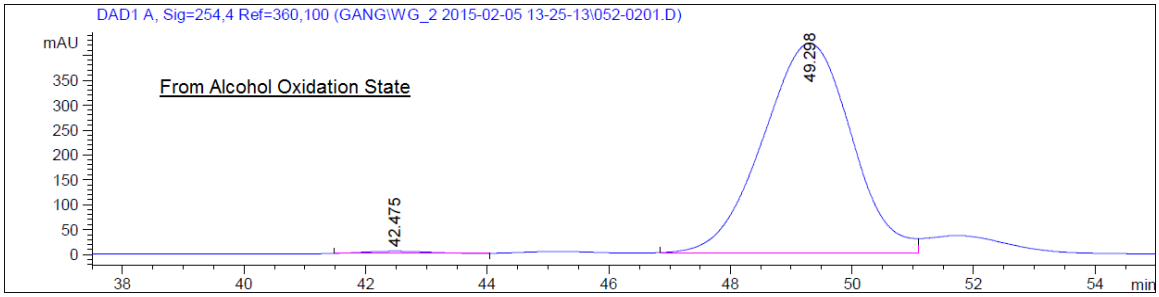
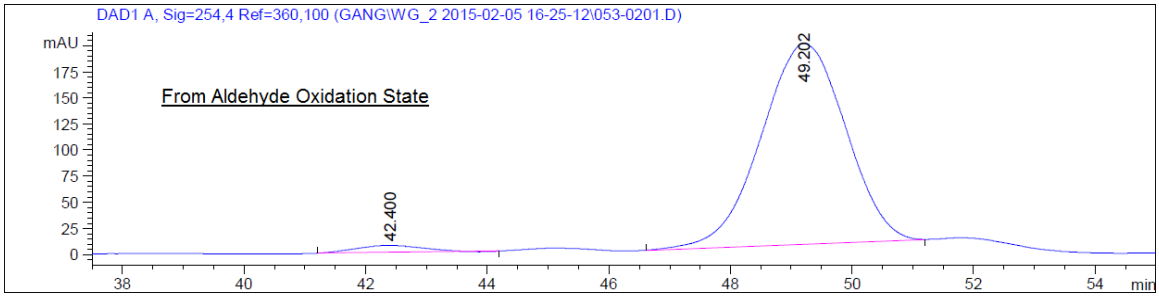
BnO
NHNs
2.08
2.02
4.93
1.00
0.95
1.02
1.01
1.95
0.97
1.04
1.00
0.94
1.05
1.00
0.98
1.04
1.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
150.08
146.14
137.50
134.35
128.73
124.46
119.50
73.68
69.90
48.57
45.19
33.62
29.84
OH
BnO
NHNs
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.901	MF	1.4631	5921.49365	67.45199	42.0820
2	44.545	MF	1.7361	1036.15869	9.94739	7.3636
3	48.483	MF	1.6766	6035.03320	59.99233	42.8889
4	51.094	FM	1.8563	1078.63989	9.68425	7.6655
Totals :				1.40713e4	147.07596	

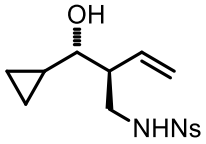


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.475	BB	0.8538	326.52264	4.49335	0.7625
2	49.298	BV	1.5576	4.24980e4	421.01926	99.2375
Totals :				4.28245e4	425.51261	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.400	BB	0.8932	488.20288	6.44896	2.5666
2	49.202	BV	1.4152	1.85333e4	192.50256	97.4334
Totals :				1.90215e4	198.95152	

***N*-((*S*)-2-((*S*)-cyclopropyl(hydroxy)methyl)but-3-en-1-yl)-4-nitrobenzenesulfonamide (3.4l)**



<u>*From alcohol oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with cyclopropylmethanol (7.2 mg, 0.1 mmol, 100 mol%), the product **3.4l** was obtained as gel in 64% yields (20.8 mg, 0.064 mmol, *anti:syn*=4:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). <u>*From aldehyde oxidation level:*</u> According to general procedure for coupling of vinyl aziridine (**3.3a**) with cyclopropanecarbaldehyde (7.0 mg, 0.1 mmol, 100 mol%), the product **3.4l** was obtained as gel in 63% yields (20.5 mg, 0.063 mmol, *anti:syn*=4:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1). Spectral data is reported for the major isomer.

<u>^{1}H NMR (400 MHz, $CDCl_3$)</u> δ 8.37 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 5.76 (ddd, *J* = 17.3, 10.3, 9.2 Hz, 1H), 5.26–5.10 (m, 3H), 3.32 (ddd, *J* = 12.5, 7.5, 6.4 Hz, 1H), 3.05 (ddd, *J* = 12.3, 7.2, 4.2 Hz, 1H), 2.87 (dd, *J* = 9.1, 3.2 Hz, 1H), 2.44 (ddd, *J* = 12.9, 8.3, 5.1 Hz, 1H), 1.66 (brs, 1H), 0.98–0.86 (m, 1H), 0.62–0.47 (m, 2H), 0.28 (dt, *J* = 8.6, 3.6 Hz, 1H), 0.18 (dt, *J* = 10.5, 2.9 Hz, 1H).

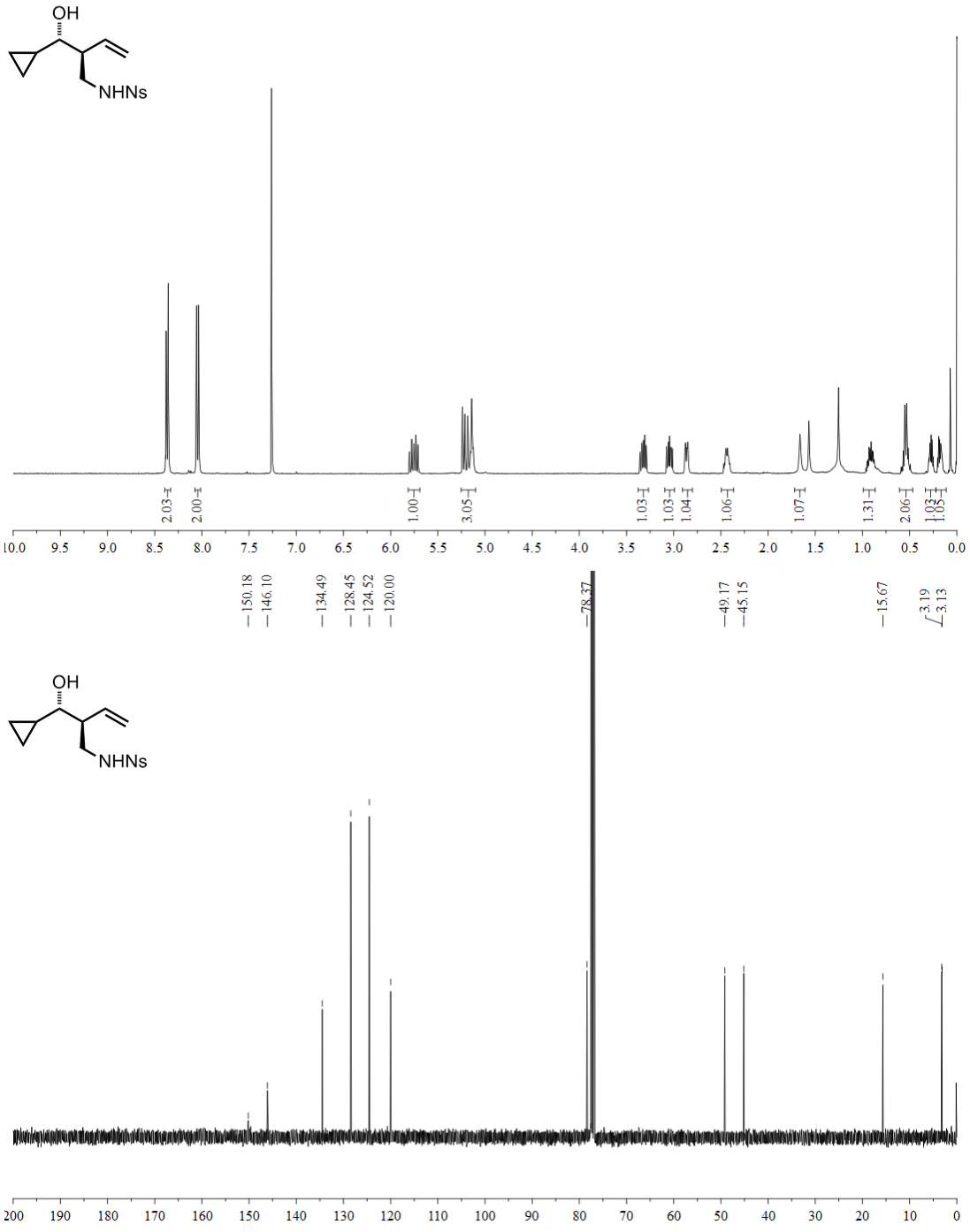
<u>^{13}C NMR (100 MHz, $CDCl_3$)</u> δ 150.2, 146.1, 134.5, 128.5, 124.5, 120.0, 78.4, 49.2, 45.2, 15.7, 3.2, 3.1.

<u>HRMS</u> (CI) Calcd. for $C_{14}H_{18}N_2O_5SNa$ $[M+Na]^+$: 349.0829, Found: 349.0830.

<u>FTIR</u> (neat): 3288, 3106, 2923, 1607, 1527, 1402, 1348, 1161, 920, 854 cm^{-1}.

<u>HPLC</u>: (Chiralcel AD-H column, hexanes:*i*-PrOH = 87:13, 1.00 mL/min, 254 nm), *ee* =95% from cyclopropylmethanol, *ee* = 98% from cyclopropanecarbaldehyde.

<u>$[\alpha]^{20}_D$ =</u> +4.00 ° (c 1.00, $CHCl_3$).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2.00
1.00
3.05
1.03
1.03
1.04
1.06
1.07
1.31
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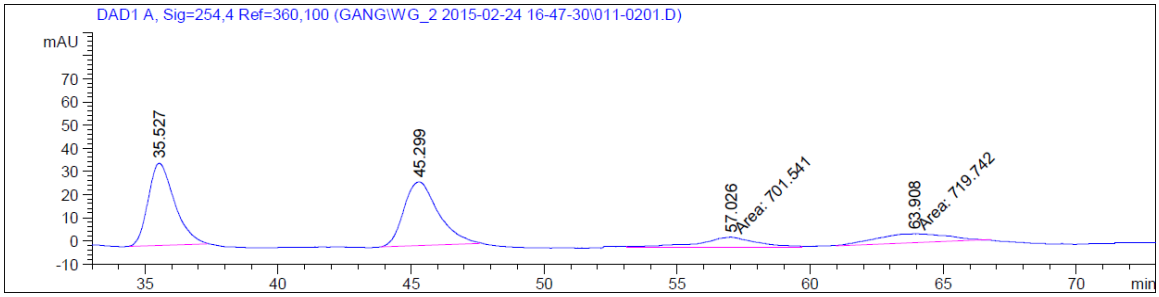
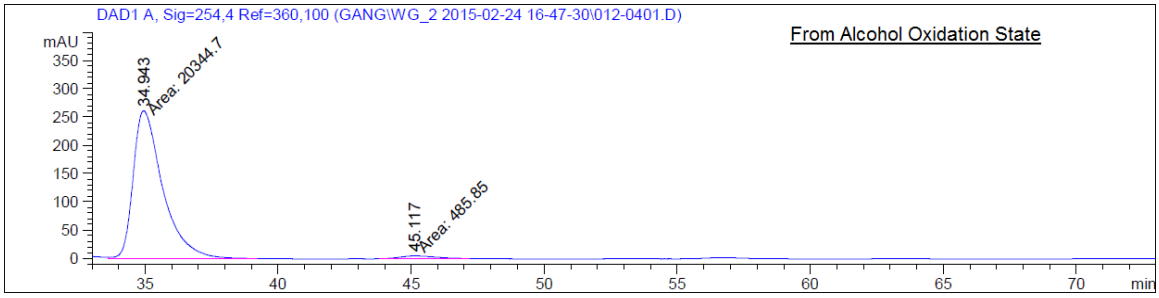
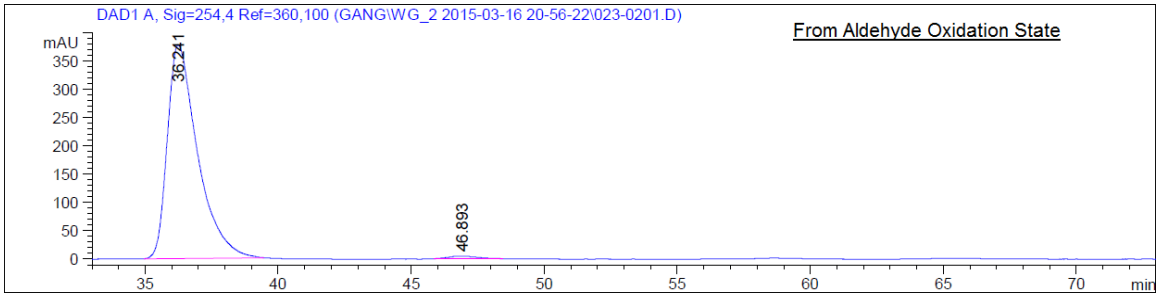
1.03
1.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
150.18
146.10
134.49
128.45
124.52
120.00
78.37
49.17
45.15
15.67
3.19
3.13
OH
NHNs
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.527	BB	0.9531	2447.08496	35.45895	38.5021
2	45.299	BB	1.0792	2487.34790	27.55417	39.1356
3	57.026	MM	2.6437	701.54108	4.42269	11.0380
4	63.908	MM	3.1143	719.74207	3.85187	11.3243
Totals :				6355.71600	71.28767	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.943	MF	1.2942	2.03447e4	262.00500	97.6676
2	45.117	FM	1.5650	485.84955	5.17415	2.3324
Totals :				2.08306e4	267.17915	

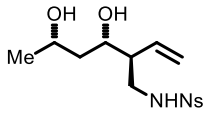


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.241	BB	1.1638	2.99097e4	377.72559	98.8785
2	46.893	BB	0.9295	339.24435	4.27648	1.1215
Totals :				3.02490e4	382.00207	

General Procedure and Spectral Data for Coupling of Vinyl Aziridine and Diols (3.2m-3.2o)

A flame-dried pressure tube equipped with a magnetic stir bar was charged with K_3PO_4 (1.1 mg, 0.005 mmol, 5 mol%), Ir-catalyst (0.005 mmol, 5 mol%), diol (0.10 mmol, 100 mol%) and 1-((4-nitrophenyl)sulfonyl)-2-vinylaziridine **3.3a** (76.3 mg, 0.30 mmol, 300 mol%). The reaction vessel was placed under an atmosphere of argon, and THF (0.5 mL, 0.2 M) was added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 80 °C for 48 h. The reaction was allowed to reach ambient temperature and concentrated *in vacuo*. The residue was subjected to column chromatography to furnish the title compound.

***N*-((2*S*,3*S*,5*S*)-3,5-dihydroxy-2-vinylhexyl)-4-nitrobenzenesulfonamide (*syn*-3.4m)**



According to general procedure for coupling of vinyl aziridine (**3.3a**) with (*S*)-butane-1,3-diol (9.0 mg, 0.1 mmol, 100 mol%), in the presence of (*R*)-Ir-3-**Vb** (5.31 mg, 0.005 mmol, 5 mol%), the product *syn*-**3.4m** was obtained as gel in 60% yields (20.7 mg, 0.060 mmol, *dr*=6:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 4:1-1:1). Spectral data is reported for the major isomer.

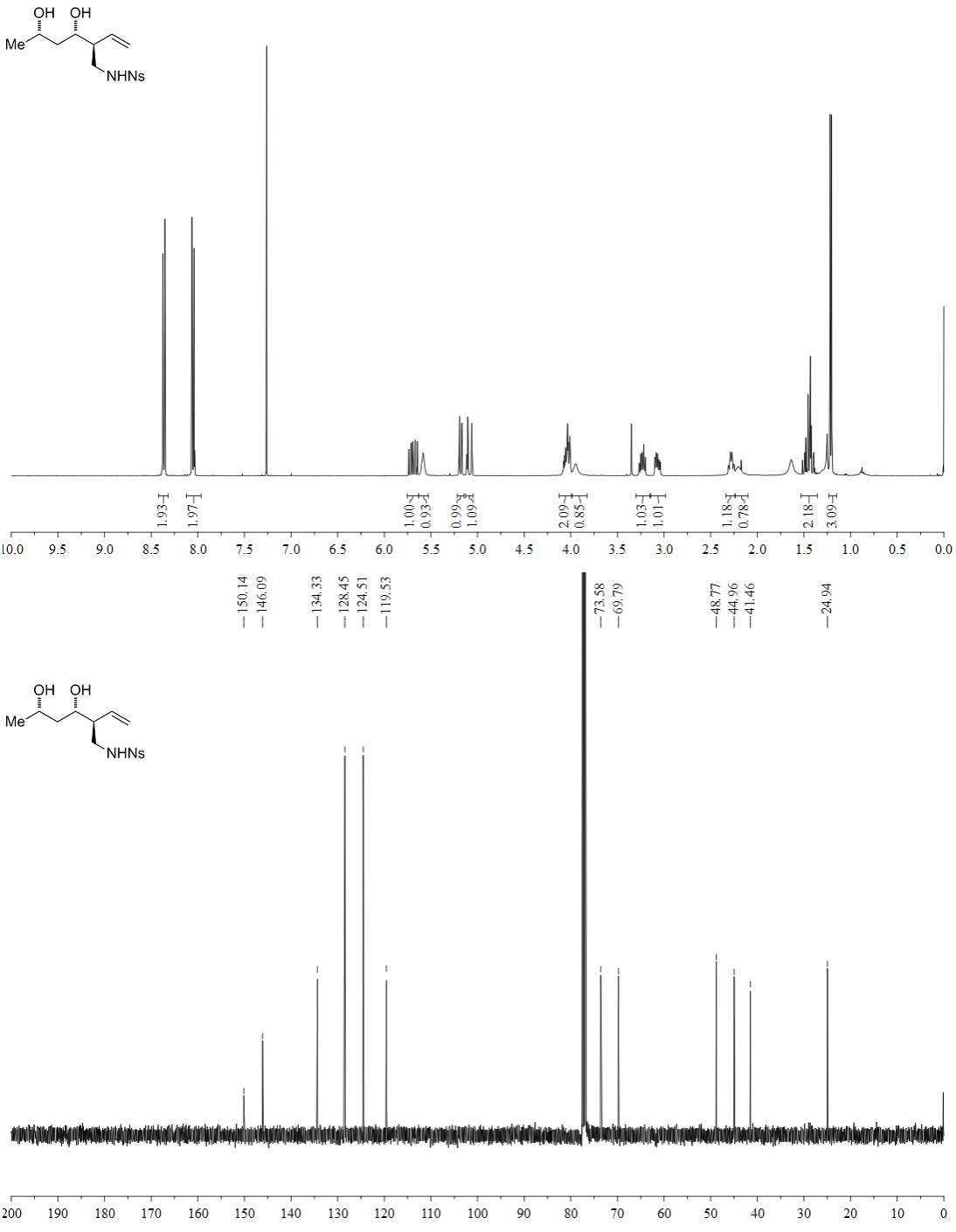
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 9.0 Hz, 2H), 5.69 (ddd, *J* = 17.3, 10.4, 8.8 Hz, 1H), 5.59 (s, 1H), 5.18 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.09 (ddd, *J* = 17.3, 1.5, 0.9 Hz, 1H), 4.05 (ddt, *J* = 9.6, 5.5, 3.1 Hz, 2H), 3.95 (s, 1H), 3.28–3.17 (m, 1H), 3.07 (ddd, *J* = 12.5, 6.1, 4.6 Hz, 1H), 2.35–2.24 (m, 1H), 2.21 (s, 1H), 1.53–1.36 (m, 2H), 1.21 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 146.1, 134.3, 128.5, 124.5, 119.5, 73.6, 69.8, 48.8, 44.9, 41.5, 24.9.

LRMS (ESI) Calcd. for $C_{14}H_{20}N_2O_6SNa$ $[M+Na]^+$: 367.1, Found: 367.1.

FTIR (neat): 3295, 2961, 2924, 2852, 2323, 1530, 1349, 1163, 928, 854 cm^{-1}.

$[\alpha]^{20}_D$ = -8.64 ° (c 0.27, EtOAc).


OH
OH
Me
NHNs
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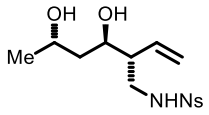
1.97
1.00
0.93
0.99
1.09
2.09
0.85
1.03
1.01
1.18
0.78
2.18
3.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
150.14
146.09
134.33
128.45
124.51
119.53
73.58
69.79
48.77
44.96
41.46
24.94
OH
OH
Me
NHNs
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

***N*-((2*R*,3*R*,5*S*)-3,5-dihydroxy-2-vinylhexyl)-4-nitrobenzenesulfonamide (*anti*-3.4m)**



According to general procedure for coupling of vinyl aziridine (**3.3a**) with (*S*)-butane-1,3-diol (9.0 mg, 0.1 mmol, 100 mol%), in the presence of (*S*)-Ir-3-**Vb** (5.31 mg, 0.005 mmol, 5 mol%), the product *anti*-**3.4m** was obtained as yellow solid in 62% yields (21.3 mg, 0.062 mmol, *dr*=5:1) after flash chromatography (SiO_2: hexane/ethyl acetate, 4:1-1:1). Spectral data is reported for the major isomer.

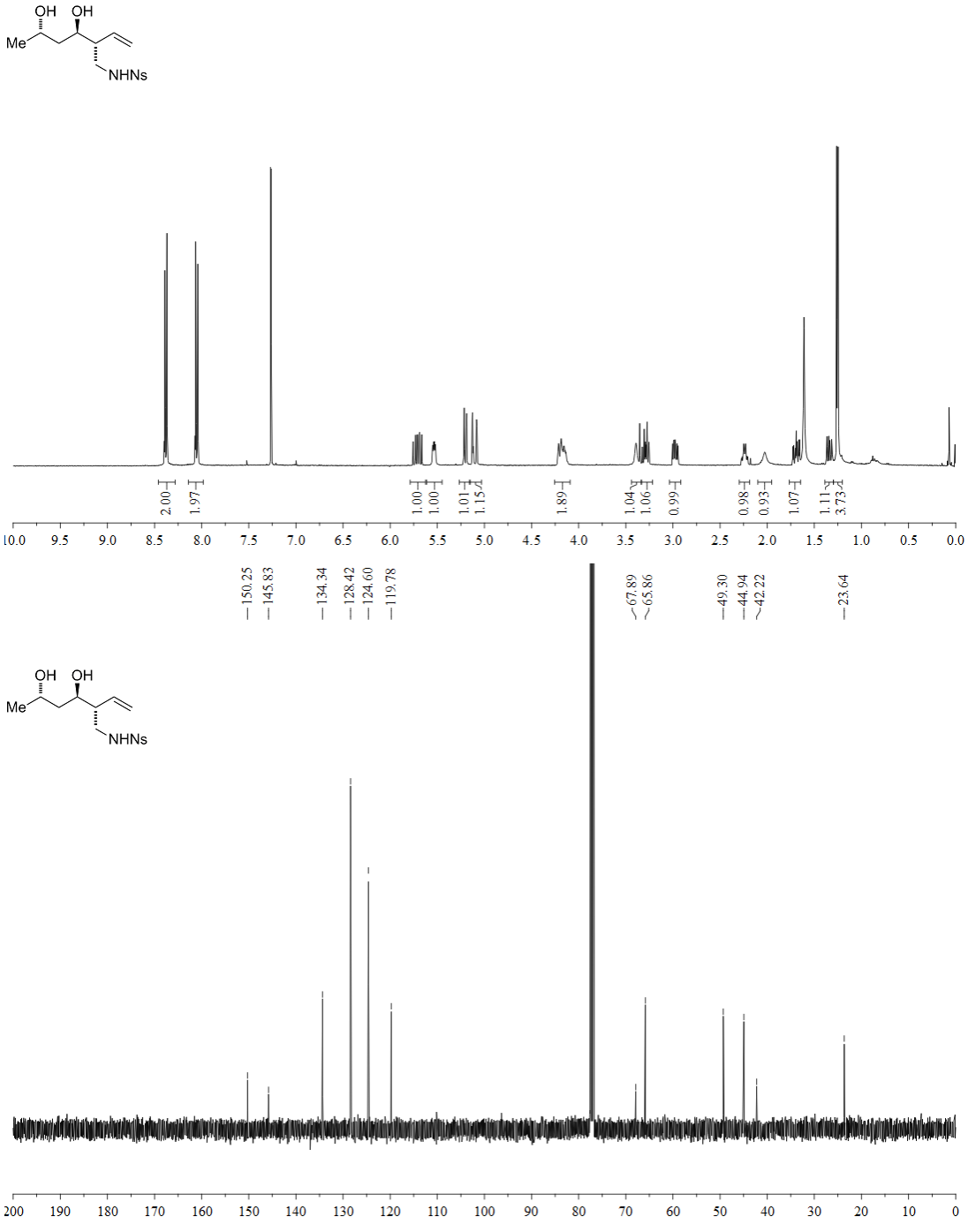
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 9.0 Hz, 2H), 5.71 (ddd, *J* = 17.3, 10.4, 9.0 Hz, 1H), 5.53 (dd, *J* = 7.8, 3.9 Hz, 1H), 5.20 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.10 (ddd, *J* = 17.3, 1.6, 0.8 Hz, 1H), 4.23–4.11 (m, 2H), 3.39 (s, 1H), 3.29 (dt, *J* = 12.4, 7.8 Hz, 1H), 2.98 (ddd, *J* = 12.3, 6.1, 3.9 Hz, 1H), 2.24 (td, *J* = 8.7, 2.9 Hz, 1H), 2.03 (s, 1H), 1.69 (ddd, *J* = 14.0, 10.6, 3.2 Hz, 1H), 1.34 (ddd, *J* = 14.5, 7.6, 2.2 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 145.8, 134.3, 128.4, 124.6, 119.8, 67.9, 65.9, 49.3, 44.9, 42.2, 23.6.

LRMS (ESI) Calcd. for $C_{14}H_{20}N_2O_6SNa$ $[M+Na]^+$: 367.1, Found: 367.1.

FTIR (neat): 3346, 3241, 2919, 1529, 1105, 1310, 1091, 1061, 937, 847 cm^{-1}.

$[\alpha]^{20}_D$ = -1.33 ° (c 0.25, EtOAc). **mp**: 105-112 ºC.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1.00
1.00
1.01
1.15
1.89
1.04
1.06
0.99
0.98
0.93
1.07
1.11
3.73
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
150.25
145.83
134.34
128.42
124.60
119.78
67.89
65.86
49.30
44.94
42.22
23.64
OH
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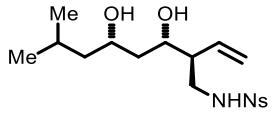
Me
NHNs
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

***N*-((2*S*,3*S*,5*S*)-3,5-dihydroxy-7-methyl-2-vinyloctyl)-4-nitrobenzenesulfonamide (*syn*-3.4n)**



According to general procedure for coupling of vinyl aziridine (**3.3a**) with (*S*)-5-methylhexane-1,3-diol (13.2 mg, 0.1 mmol, 100 mol%), in the presence of (*R*)-Ir-3-**Ib** (5.17 mg, 0.005 mmol, 5 mol%), the product *syn*-**3.4n** was obtained as gel in 67% yields (25.8 mg, 0.067 mmol, *dr*=7:1) after flash chromatography (SiO_2: dichloromethane/methanol, 100:1-80:1). Spectral data is reported for the major isomer.

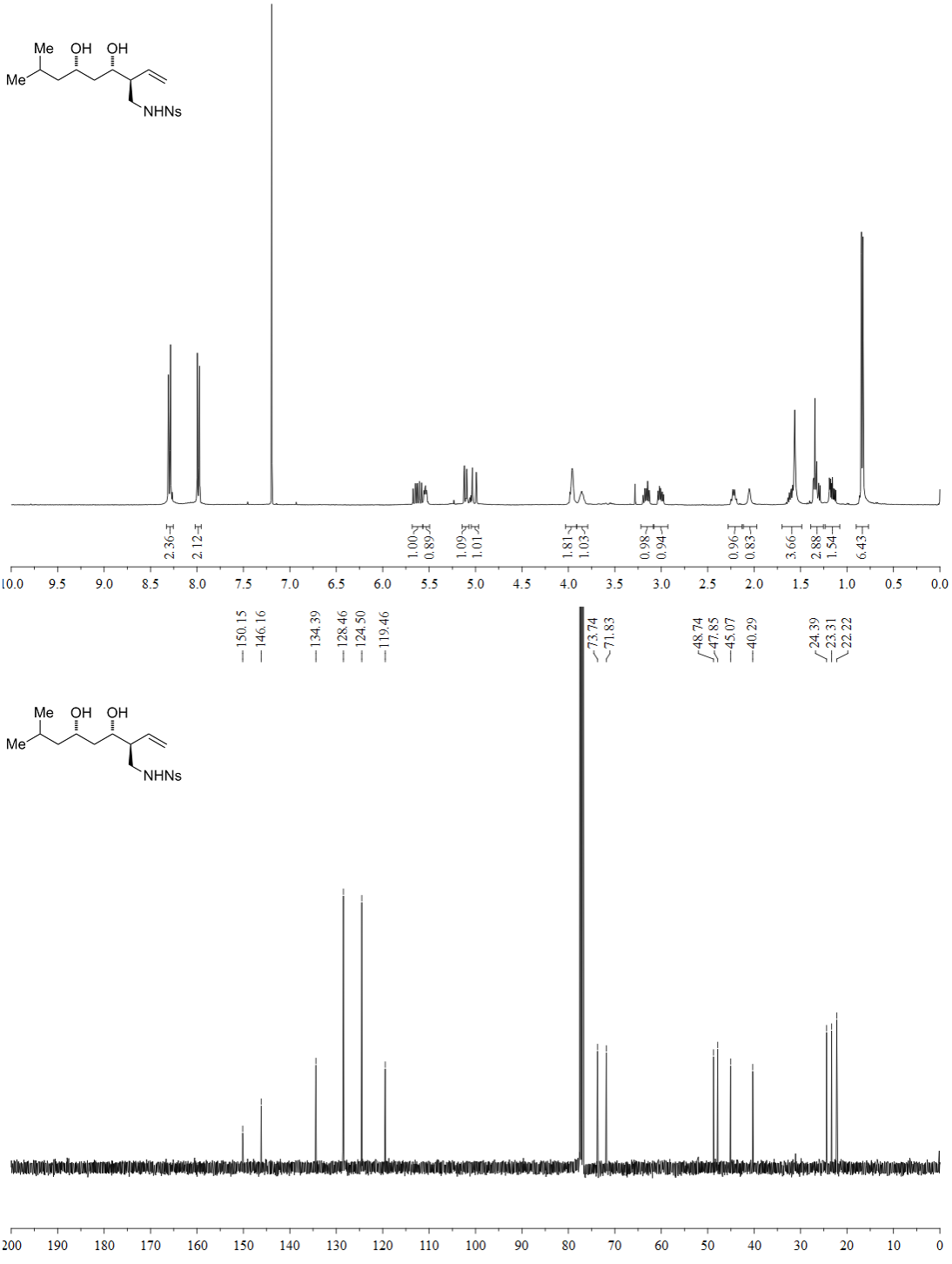
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 9.0 Hz, 2H), 5.69 (ddd, *J* = 17.3, 10.4, 8.8 Hz, 1H), 5.63–5.58 (m, 1H), 5.17 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.08 (ddd, *J* = 17.3, 1.6, 0.9 Hz, 1H), 4.03 (dd, *J* = 10.6, 4.3 Hz, 2H), 3.92 (s, 1H), 3.27–3.18 (m, 1H), 3.07 (ddd, *J* = 12.5, 6.1, 4.7 Hz, 1H), 2.28 (td, *J* = 8.9, 2.7 Hz, 1H), 2.12 (s, 1H), 1.74–1.64 (m, 1H), 1.45–1.34 (m, 3H), 1.28–1.17 (m, 1H), 0.90 (dd, *J* = 6.6, 1.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 146.2, 134.4, 128.5, 124.5, 119.5, 73.7, 71.8, 48.7, 47.9, 45.1, 40.3, 24.4, 23.3, 22.2.

LRMS (ESI) Calcd. for $C_{17}H_{26}N_2O_6SNa$ $[M+Na]^+$: 409.1, Found: 409.1.

FTIR (neat): 2955, 2925, 2869, 2322, 2282, 1531, 1012, 929, 855 cm^{-1}.

$[\alpha]^{20}_D$ = -5.20 ° (c 0.24, EtOAc).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OH
Me
NHNs
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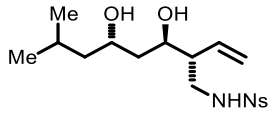
2.12
1.00
0.89
1.09
1.01
1.81
1.03
0.98
0.94
0.96
0.83
3.66
2.88
1.54
6.43
150.15
146.16
134.39
128.46
124.50
119.46
73.74
71.83
48.74
47.85
45.07
40.29
24.39
23.31
22.22

***N*-((2*R*,3*R*,5*S*)-3,5-dihydroxy-7-methyl-2-vinyloctyl)-4-nitrobenzenesulfonamide (*anti*-3.4n)**



According to general procedure for coupling of vinyl aziridine (**3.3a**) with (*S*)-5-methylhexane-1,3-diol (13.2 mg, 0.1 mmol, 100 mol%), in the presence of (*S*)-Ir-3-**Ib** (5.17 mg, 0.005 mmol, 5 mol%), the product *anti*-**3.4n** was obtained as yellow solid in 68% yields (26.2 mg, 0.068 mmol, *dr*=4:1) after flash chromatography (SiO_2: dichloromethane/methanol, 100:1-80:1). Spectral data is reported for the major isomer.

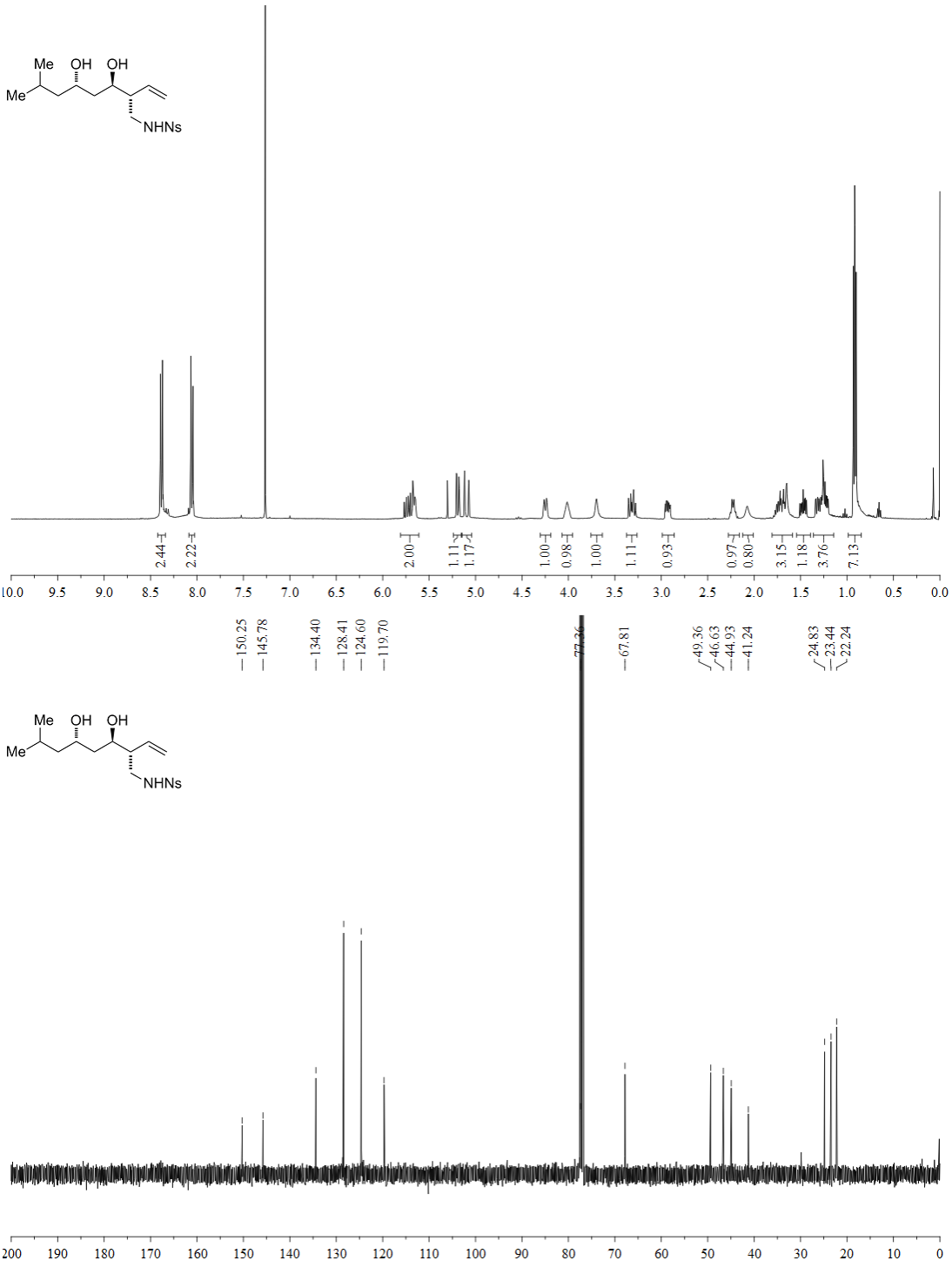
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 9.0 Hz, 2H), 5.78–5.62 (m, 2H), 5.19 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.13–5.05 (m, 1H), 4.25 (d, *J* = 10.2 Hz, 1H), 4.01 (s, 1H), 3.70 (s, 1H), 3.36–3.26 (m, 1H), 2.93 (ddd, *J* = 12.1, 5.7, 3.6 Hz, 1H), 2.23 (qd, *J* = 8.4, 2.6 Hz, 1H), 2.07 (s, 1H), 1.81–1.62 (m, 2H), 1.47 (ddd, *J* = 14.4, 9.0, 5.6 Hz, 1H), 1.36–1.19 (m, 2H), 0.92 (dd, *J* = 6.5, 5.5 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 145.8, 134.4, 128.4, 124.6, 119.7, 77.4, 67.8, 49.4, 46.6, 44.9, 41.2, 24.8, 23.4, 22.2.

LRMS (ESI) Calcd. for $C_{17}H_{26}N_2O_6SNa$ $[M+Na]^+$: 409.1, Found: 409.1.

FTIR (neat): 2951, 2924, 2869, 2359, 2223, 1606, 1464, 1310, 925, 855 cm^{-1}.

$[\alpha]^{20}_D$ = -16.00 ° (c 0.25, EtOAc). **mp**: 136-138 ºC.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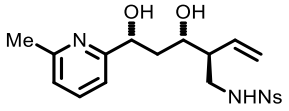
Me
NHNs
2.44
2.22
2.00
1.11
1.17
1.00
0.98
1.00
1.11
0.93
0.97
0.80
3.15
1.18
3.76
7.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
150.25
145.78
134.40
128.41
124.60
119.70
77.26
67.81
49.36
46.63
44.93
41.24
24.83
23.44
22.24
Me
OH
OH
Me
NHNs
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

***N*-((2*S*,3*S*,5*R*)-3,5-dihydroxy-5-(6-methylpyridin-2-yl)-2-vinylpentyl)-4-nitrobenzene-sulfonamide (*syn*-3.4o)**



According to general procedure for coupling of vinyl aziridine (**3.3a**) with (*R*)-1-(6-methylpyridin-2-yl)propane-1,3-diol (16.7 mg, 0.1 mmol, 100 mol%), in the presence of (*R*)-Ir-3-**Vb** (5.31 mg, 0.005 mmol, 5 mol%), the product *syn*-**3.4o** was obtained as gel in 65% yields (27.4 mg, 0.065 mmol, *dr*=4:1) after flash chromatography (SiO_2: dichloromethane/methanol, 100:1-80:1). Spectral data is reported for the major isomer.

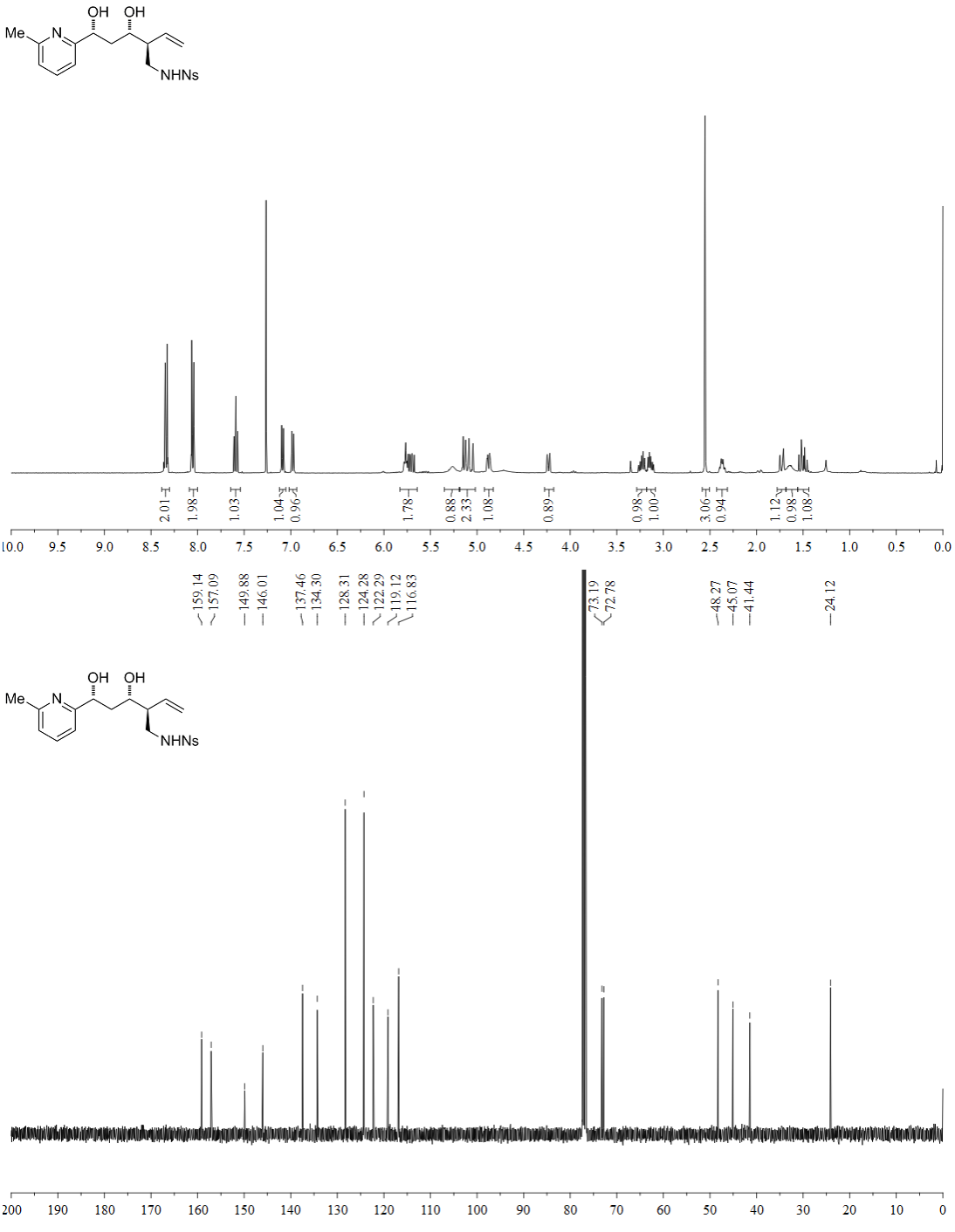
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 5.77 (t, *J* = 5.4 Hz, 1H), 5.75–5.67 (m, 1H), 5.26 (brs, 1H), 5.17–5.02 (m, 2H), 4.88 (dd, *J* = 10.5, 2.7 Hz, 1H), 4.27–4.19 (m, 1H), 3.28–3.19 (m, 1H), 3.18–3.08 (m, 1H), 2.55 (s, 3H), 2.37 (td, *J* = 8.9, 2.9 Hz, 1H), 1.73 (ddd, *J* = 14.2, 2.9, 1.7 Hz, 1H), 1.64 (s, 1H), 1.50 (dt, *J* = 14.3, 10.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 157.2, 150.0, 146.2, 137.6, 134.5, 128.5, 124.4, 122.5, 119.3, 116.9, 73.3, 72.9, 48.4, 45.2, 41.6, 24.3.

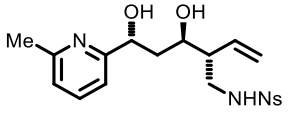
LRMS (ESI) Calcd. for $C_{19}H_{23}N_3O_6SNa$ $[M+Na]^+$: 444.1, Found: 444.1.

FTIR (neat): 3368, 2927, 1597, 1577, 1558, 1530, 1460, 1310, 1011, 854 cm^{-1}.

$[\alpha]^{20}_D$ = +2.61 ° (c 0.64, $CHCl_3$).


OH
OH
Me
N
NHNs
2.01
1.98
1.03
1.04
0.96
1.78
0.88
2.33
1.08
0.89
0.98
1.00
3.06
0.94
1.12
0.98
1.08
159.14
157.09
149.88
146.01
137.46
134.30
128.31
124.28
122.29
119.12
116.83
73.19
72.78
48.27
45.07
41.44
24.12

***N*-((2*R*,3*R*,5*R*)-3,5-dihydroxy-5-(6-methylpyridin-2-yl)-2-vinylpentyl)-4-nitrobenzene-sulfonamide (*anti*-3.4o)**



According to general procedure for coupling of vinyl aziridine (**3.3a**) with (*R*)-1-(6-methylpyridin-2-yl)propane-1,3-diol (16.7 mg, 0.1 mmol, 100 mol%), in the presence of (*S*)-Ir-3-**Vb** (5.31 mg, 0.005 mmol, 5 mol%), the product *anti*-**3.4o** was obtained as gel in 62% yields (26.1 mg, 0.062 mmol, *dr*=4:1) after flash chromatography (SiO_2: dichloromethane/methanol, 100:1-80:1). Spectral data is reported for the major isomer.

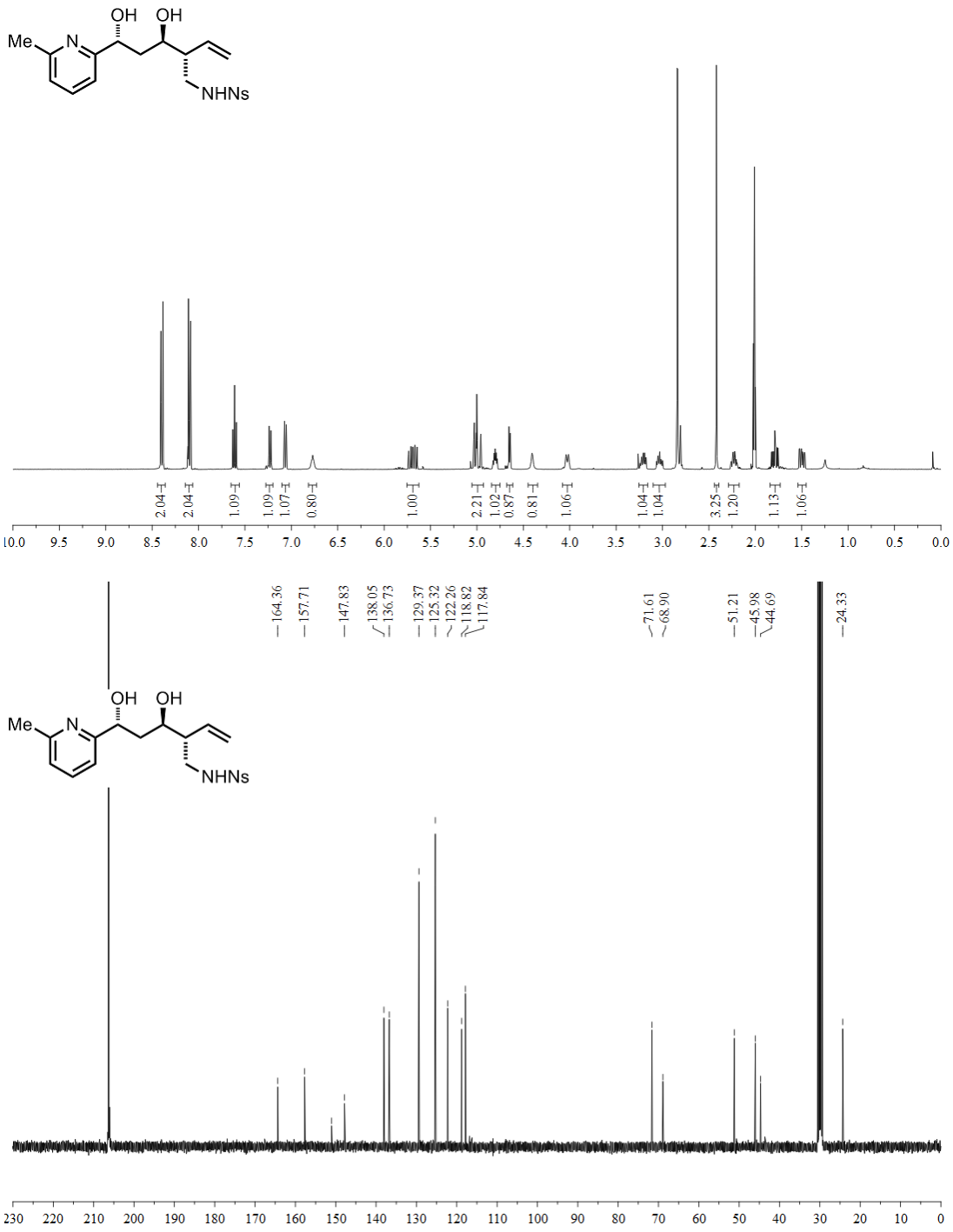
^{1}H NMR (400 MHz, CD_3COCD_3) δ 8.31 (d, *J* = 9.0 Hz, 2H), 8.01 (d, *J* = 9.0 Hz, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.68 (s, 1H), 5.60 (ddd, *J* = 17.3, 10.4, 9.1 Hz, 1H), 4.97–4.85 (m, 2H), 4.76–4.66 (m, 1H), 4.56 (d, *J* = 5.3 Hz, 1H), 4.32 (brs, 1H), 3.94 (d, *J* = 10.0 Hz, 1H), 3.12 (dt, *J* = 12.5, 6.1 Hz, 1H), 2.99–2.88 (m, 1H), 2.33 (s, 3H), 2.14 (td, *J* = 9.5, 2.5 Hz, 1H), 1.70 (ddd, *J* = 14.1, 10.2, 3.8 Hz, 1H), 1.41 (ddd, *J* = 14.1, 8.4, 2.3 Hz, 1H).

^{13}C NMR (100 MHz, CD_3COCD_3) δ 164.8, 158.1, 151.4, 148.3, 138.5, 137.2, 129.8, 125.7, 122.7, 119.2, 118.3, 72.0, 69.3, 51.6, 46.4, 45.1, 24.8.

LRMS (ESI) Calcd. for $C_{19}H_{23}N_3O_6SNa$ $[M+Na]^+$: 444.1, Found: 444.1.

FTIR (neat): 3376, 3286, 2920, 2359, 1529, 1348, 1162, 924, 854 cm^{-1}.

$[\alpha]^{20}_D$ = -61.91 ° (c 0.14, $CHCl_3$). **mp:** 156-158 °C.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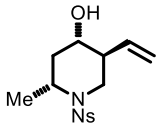
1.09
1.09
1.07
0.80
1.00
2.21
1.02
0.87
0.81
1.06
1.04
1.04
3.25
1.20
1.13
1.06
164.36
157.71
147.83
138.05
136.73
129.37
125.32
122.26
118.82
117.84
71.61
68.90
51.21
45.98
44.69
24.33

General Procedure and Spectral Data for Mitsunobu Reaction to Form Piperidines (3.5m-3.5o)

A flame-dried flask equipped with a magnetic stir bar was charged **3.4m**, **3.4n** or **3.4o** (0.05 mmol, 100 mol%) in 0.5 mL dichloromethane (0.1 M). Triphenylphosphine (19.7 mg, 0.075 mmol, 150 mol%) and DIAD (disisopropyl azodicarboxylate, 15.2 mg, 0.075 mmol, 150 mol%) were added at 0 ºC. The flask was capped and the reaction mixture was allowed to stir at r.t. for 16 h. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography to furnish the title compound.

(2*R*,4*S*,5*S*)-2-methyl-1-((4-nitrophenyl)sulfonyl)-5-vinylpiperidin-4-ol (*syn*-3.5m)



According to general procedure with *syn*-**3.4m** (17.2 mg, 0.05 mmol, 100 mol%), triphenylphosphine (19.7 mg, 0.075 mmol, 150 mol%) and DIAD (15.2 mg, 0.075 mmol, 150 mol%), the product *syn*-**3.5m** was obtained as gel in 80% yields (13.1 mg, 0.040 mmol) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1).

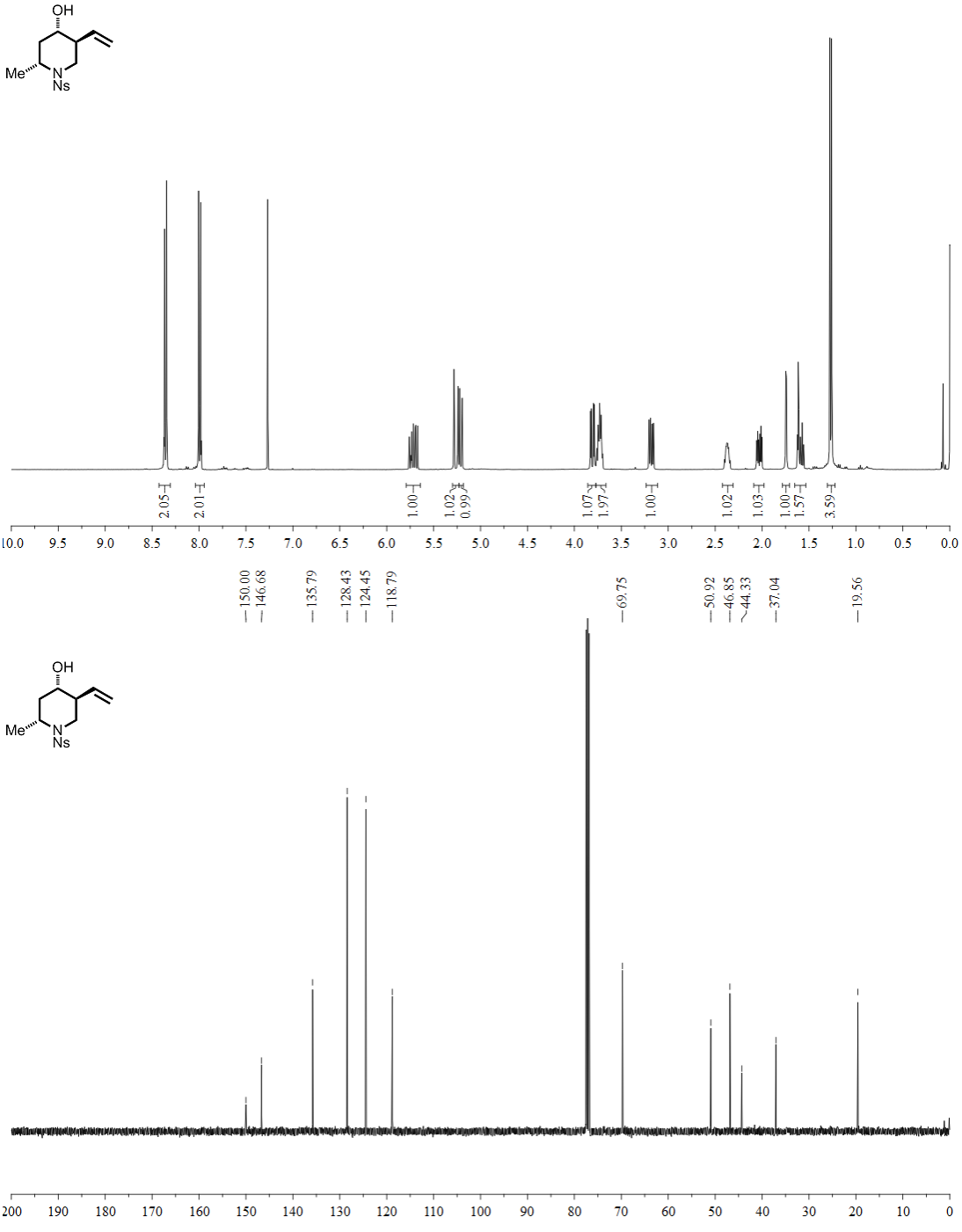
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.0 Hz, 2H), 7.99 (d, *J* = 9.1 Hz, 2H), 5.71 (ddd, *J* = 17.3, 10.4, 8.0 Hz, 1H), 5.26 (dt, *J* = 17.3, 1.3 Hz, 1H), 5.23–5.18 (m, 1H), 3.81 (dd, *J* = 12.8, 3.6 Hz, 1H), 3.77–3.69 (m, 2H), 3.18 (dd, *J* = 12.8, 5.9 Hz, 1H), 2.42–2.31 (m, 1H), 2.03 (ddd, *J* = 14.0, 4.8, 4.0 Hz, 1H), 1.74 (d, *J* = 2.9 Hz, 1H), 1.65–1.54 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.7, 135.8, 128.4, 124.5, 118.8, 69.8, 50.9, 46.9, 44.3, 37.0, 19.6.

LRMS (ESI) Calcd. for $C_{14}H_{18}N_2O_5SNa$ $[M+Na]^+$: 349.1, Found: 349.1.

FTIR (neat): 2924, 2856, 1605, 1529, 1453, 1348, 1217, 1151, 1013, 919, 855 cm^{-1}.

$[\alpha]^{20}_D$ = -1.07 ° (c 0.94, $CHCl_3$).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Me
N
Ns
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2.01
1.00
1.02
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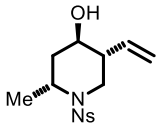
1.07
1.97
1.00
1.02
1.03
1.00
1.57
3.59
150.00
146.68
135.79
128.43
124.45
118.79
69.75
50.92
46.85
44.33
37.04
19.56

(2*R*,4*R*,5*R*)-2-methyl-1-((4-nitrophenyl)sulfonyl)-5-vinylpiperidin-4-ol (*anti*-3.5m)



According to general procedure with *anti*-**3.4m** (17.2 mg, 0.05 mmol, 100 mol%), triphenylphosphine (19.7 mg, 0.075 mmol, 150 mol%) and DIAD (15.2 mg, 0.075 mmol, 150 mol%), the product *anti*-**3.5m** was obtained as white solid in 85% yields (13.9 mg, 0.043 mmol) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.0 Hz, 2H), 8.01 (d, *J* = 9.0 Hz, 2H), 5.59 (ddd, *J* = 17.0, 10.5, 8.5 Hz, 1H), 5.33–5.24 (m, 2H), 4.48–4.39 (m, 1H), 3.84 (ddd, *J* = 13.8, 4.8, 1.2 Hz, 1H), 3.70–3.61 (m, 1H), 2.91 (dd, *J* = 13.9, 11.9 Hz, 1H), 2.04–1.93 (m, 1H), 1.89 (ddd, *J* = 13.0, 4.4, 1.9 Hz, 1H), 1.81 (d, *J* = 3.0 Hz, 1H), 1.57–1.47 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H).

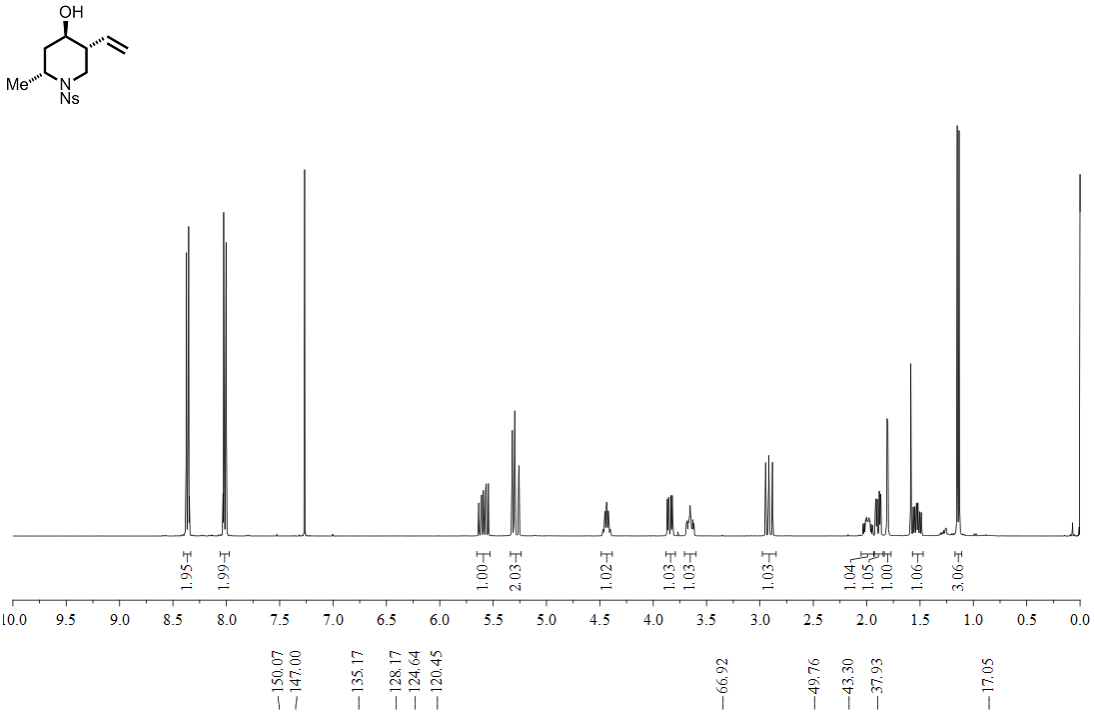
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 147.0, 135.2, 128.2, 124.6, 120.5, 66.9, 49.8, 43.3, 37.9, 17.1.

mp: 118-120 ºC.

LRMS (ESI) Calcd. for $C_{14}H_{18}N_2O_5SNa$ $[M+Na]^+$: 349.1, Found: 349.1.

FTIR (neat): 2922, 2855, 2323, 1605, 1528, 1348, 1160, 1025, 920, 854 cm^{-1}.

$[\alpha]^{20}_D$ = -43.34 ° (c 0.70, $CHCl_3$).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1.03
1.03
1.03
1.04
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3.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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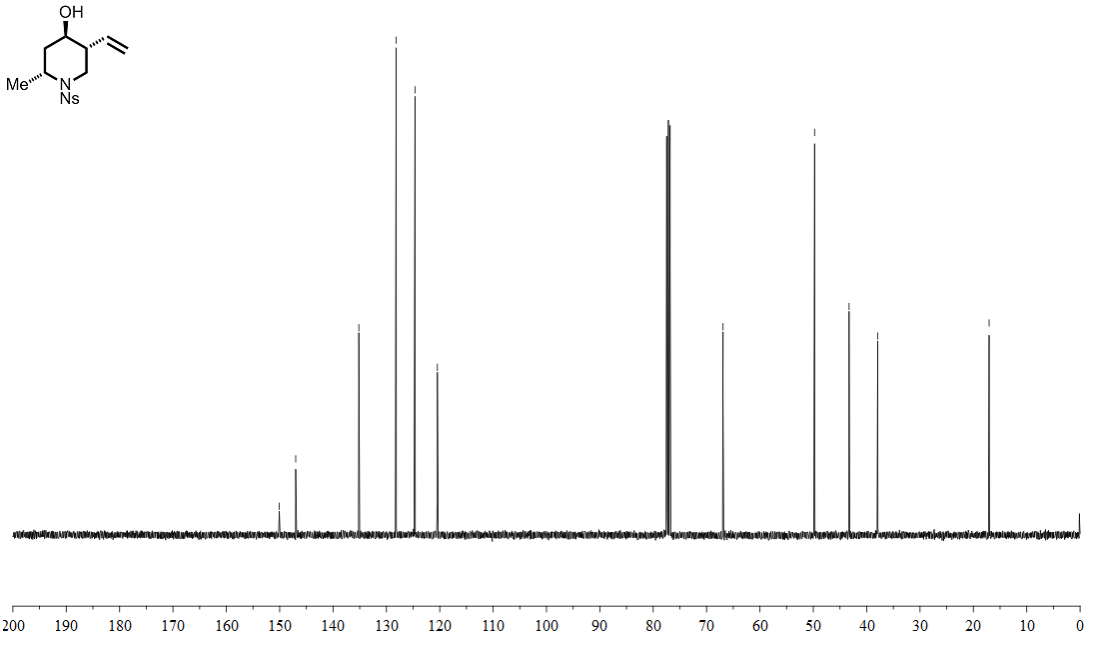
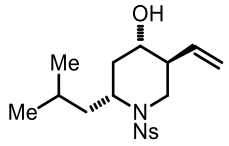
147.00
135.17
128.17
124.64
120.45
66.92
49.76
43.30
37.93
17.05


OH
Me
N
Ns
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

(2*R*,4*S*,5*S*)-2-isobutyl-1-((4-nitrophenyl)sulfonyl)-5-vinylpiperidin-4-ol (*syn*-3.5n)



According to general procedure with *syn*-**3.4n** (19.3 mg, 0.05 mmol, 100 mol%), triphenylphosphine (19.7 mg, 0.075 mmol, 150 mol%) and DIAD (15.2 mg, 0.075 mmol, 150 mol%), the product *syn*-**3.5n** was obtained as gel in 86% yields (15.8 mg, 0.043 mmol) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-3:1).

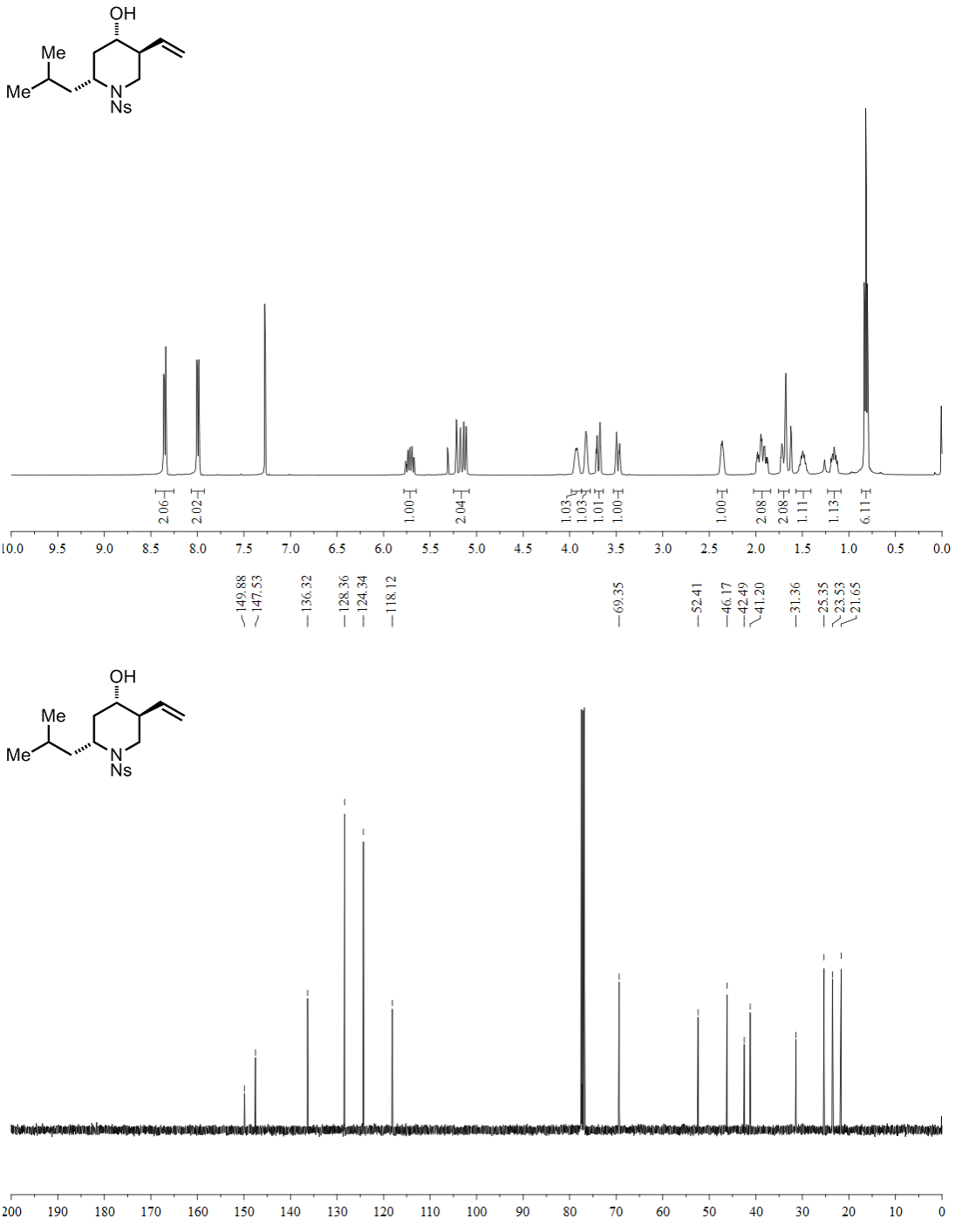
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 5.78–5.65 (m, 1H), 5.25–5.09 (m, 2H), 3.98–3.88 (m, 1H), 3.83 (s, 1H), 3.69 (dt, *J* = 13.3, 3.1 Hz, 1H), 3.48 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.37 (d, *J* = 3.6 Hz, 1H), 2.01–1.86 (m, 2H), 1.75–1.65 (m, 2H), 1.50 (dt, *J* = 11.8, 6.1 Hz, 1H), 1.16 (ddd, *J* = 13.5, 5.3, 2.6 Hz, 1H), 0.82 (td, *J* = 6.6, 3.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.5, 136.3, 128.4, 124.3, 118.1, 69.4, 52.4, 46.2, 42.5, 41.2, 31.4, 25.4, 23.5, 21.7.

LRMS (ESI) Calcd. for $C_{17}H_{24}N_2O_5SNa$ $[M+Na]^+$: 391.1, Found: 391.1.

FTIR (neat): 3540, 2956, 1605, 1528, 1347, 1305, 1150, 959, 854 cm^{-1}.

$[\alpha]^{20}_D$ = -6.33 ° (c 1.00, $CHCl_3$).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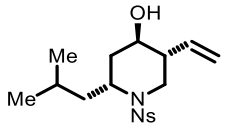
Me
Me
N
Ns
2.06
2.02
1.00
2.04
1.03
1.03
1.01
1.00
1.00
2.08
2.08
1.11
1.13
6.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
149.88
147.53
136.32
128.36
124.34
118.12
69.35
52.41
46.17
42.49
41.20
31.36
25.35
23.53
21.65
OH
Me
Me
N
Ns
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

(2*R*,4*R*,5*R*)-2-isobutyl-1-((4-nitrophenyl)sulfonyl)-5-vinylpiperidin-4-ol (*anti*-3.5n)



According to general procedure with *anti*-**3.4n** (19.3 mg, 0.05 mmol, 100 mol%), triphenylphosphine (19.7 mg, 0.075 mmol, 150 mol%) and DIAD (15.2 mg, 0.075 mmol, 150 mol%), the product *anti*-**3.5n** was obtained as gel in 62% yields (11.4 mg, 0.031 mmol) after flash chromatography (SiO_2: dichloromethane/methanol, 120:1-90:1).

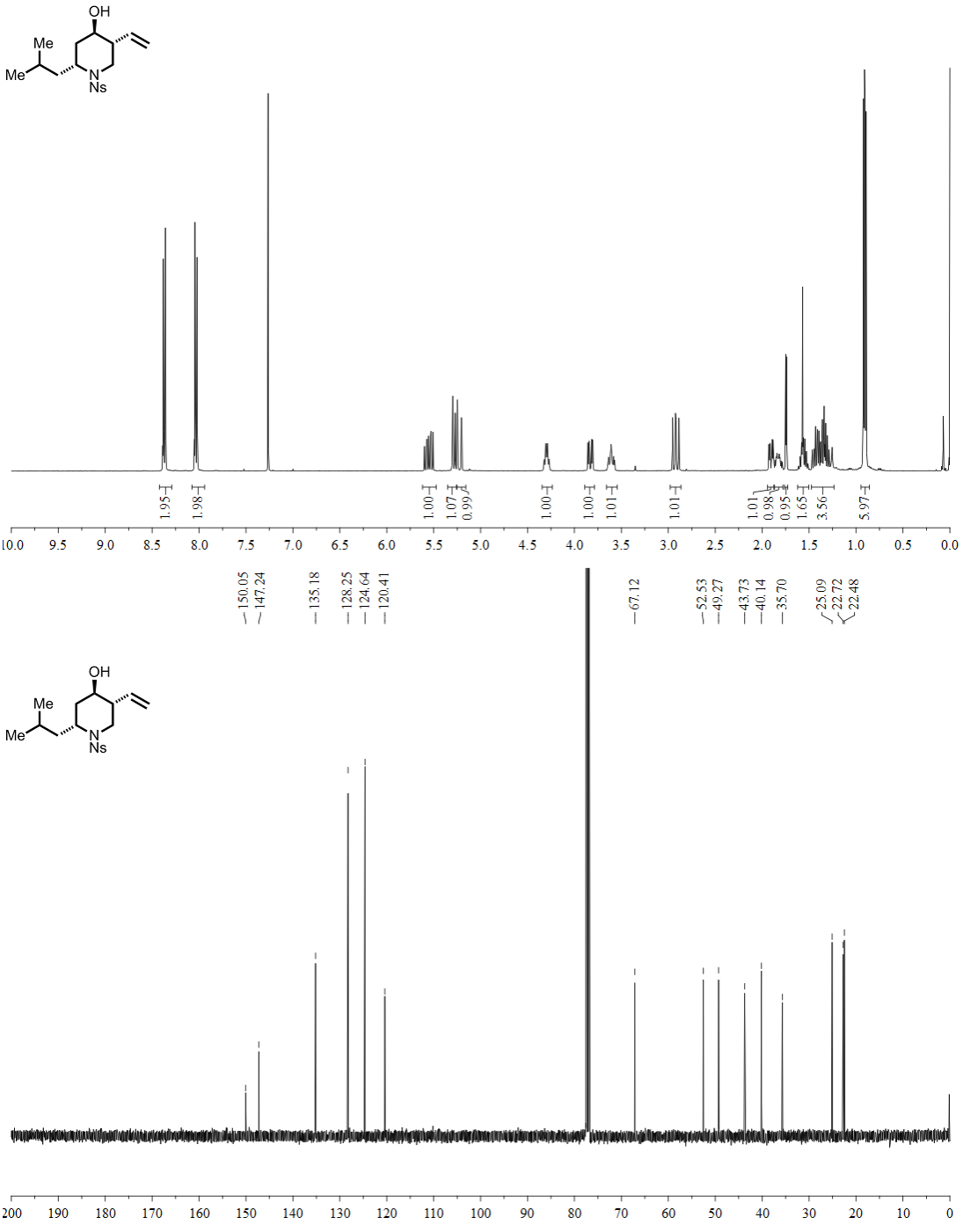
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.03 (d, *J* = 9.0 Hz, 2H), 5.55 (ddd, *J* = 17.1, 10.4, 8.5 Hz, 1H), 5.32–5.26 (m, 1H), 5.22 (ddd, *J* = 17.1, 1.4, 0.8 Hz, 1H), 4.30 (dd, *J* = 13.6, 7.0 Hz, 1H), 3.83 (ddd, *J* = 14.6, 4.8, 1.1 Hz, 1H), 3.67–3.55 (m, 1H), 2.92 (dd, *J* = 14.6, 12.0 Hz, 1H), 1.90 (ddd, *J* = 13.1, 4.4, 1.8 Hz, 1H), 1.88–1.78 (m, 1H), 1.74 (d, *J* = 3.0 Hz, 1H), 1.62–1.51 (m, 1H), 1.47–1.24 (m, 3H), 0.91 (dd, *J* = 6.6, 4.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 147.2, 135.2, 128.3, 124.6, 120.4, 67.1, 52.5, 49.3, 43.7, 40.1, 35.7, 25.1, 22.7, 22.5.

LRMS (ESI) Calcd. for $C_{17}H_{24}N_2O_5SNa$ $[M+Na]^+$: 391.1, Found: 391.1.

FTIR (neat): 3102, 2955, 2869, 2359, 1529, 1349, 1162, 989, 854 cm^{-1}.

$[\alpha]^{20}_D$ = -17.86 ° (c 0.56, $CHCl_3$).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N
Ns
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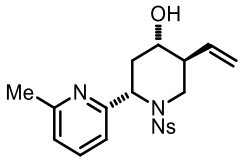
1.98
1.00
1.07
0.99
1.00
1.00
1.01
1.01
1.01
0.98
0.95
1.65
3.56
5.97
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
150.05
147.24
135.18
128.25
124.64
120.41
67.12
52.53
49.27
43.73
40.14
35.70
25.09
22.72
22.48
OH
Me
Me
N
Ns
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

(2*S*,4*S*,5*S*)-2-(6-methylpyridin-2-yl)-1-((4-nitrophenyl)sulfonyl)-5-vinylpiperidin-4-ol (*syn*-3.5o)



According to general procedure with *syn*-**3.4o** (21.0 mg, 0.05 mmol, 100 mol%), triphenylphosphine (19.7 mg, 0.075 mmol, 150 mol%) and DIAD (15.2 mg, 0.075 mmol, 150 mol%), the product *syn*-**3.5o** was obtained as gel in 70% yields (14.1 mg, 0.035 mmol) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-2:1).

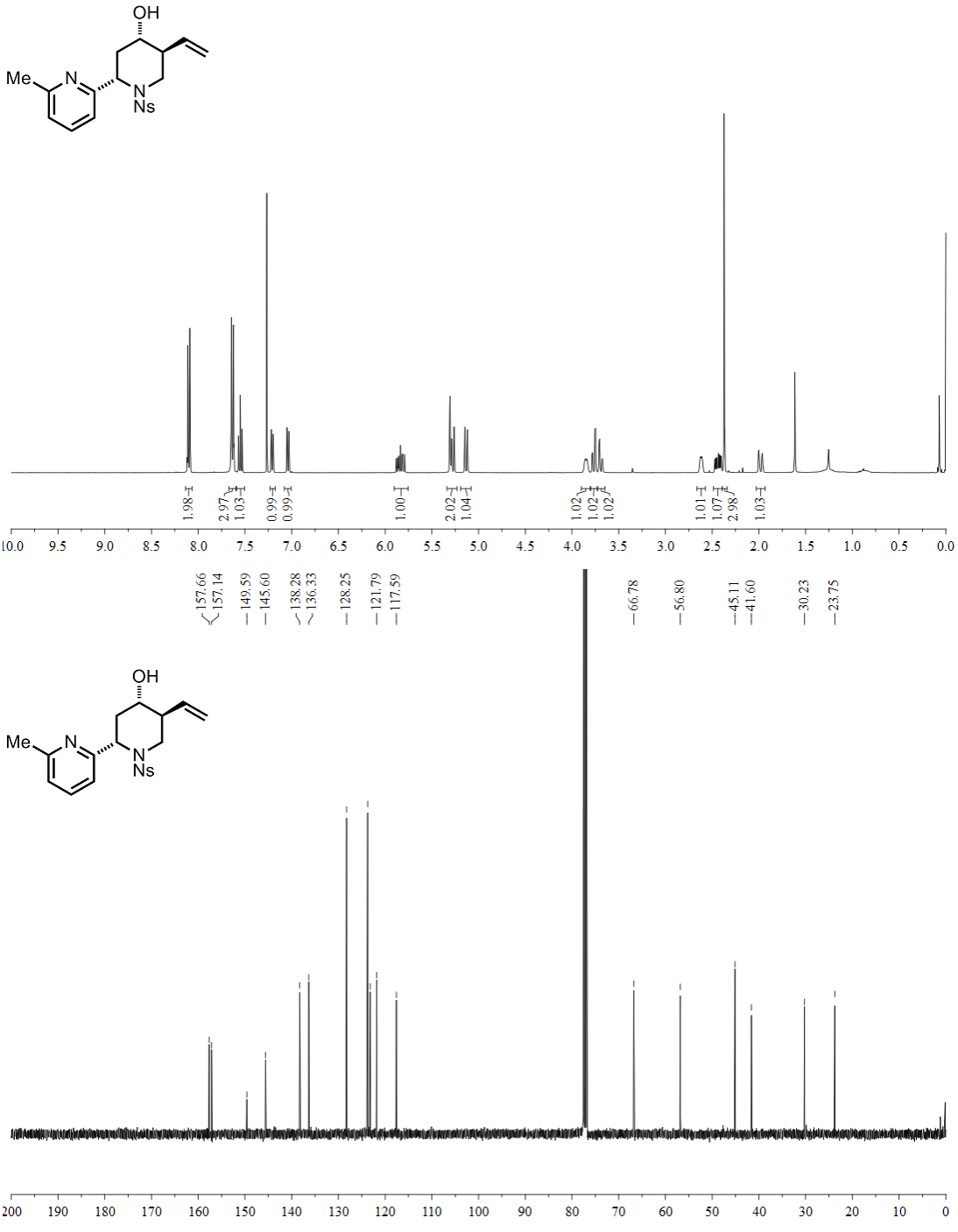
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.07–7.01 (m, 1H), 5.84 (ddd, *J* = 17.6, 10.6, 7.3 Hz, 1H), 5.32–5.24 (m, 2H), 5.13 (dt, *J* = 10.6, 1.3 Hz, 1H), 3.89–3.82 (m, 1H), 3.77 (dd, *J* = 12.8, 2.9 Hz, 1H), 3.69 (dd, *J* = 12.8, 2.3 Hz, 1H), 2.66–2.58 (m, 1H), 2.44 (ddd, *J* = 14.9, 7.9, 3.9 Hz, 1H), 2.37 (s, 3H), 2.03–1.93 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 157.1, 149.6, 145.6, 138.3, 136.3, 128.3, 123.7, 123.2, 121.8, 117.6, 66.8, 56.8, 45.1, 41.6, 30.2, 23.8.

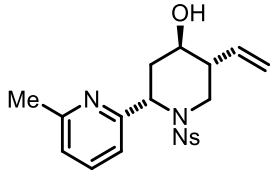
LRMS (ESI) Calcd. for $C_{19}H_{21}N_3O_5SNa$ $[M+Na]^+$: 426.1, Found: 426.1.

FTIR (neat): 2925, 2859, 1596, 1523, 1214, 1175, 1042, 908, 854 cm^{-1}.

$[\alpha]^{20}_D$ = -16.80 ° (c 1.00, $CHCl_3$).


OH
Me
N
N
Ns
1.98
2.97
1.03
0.99
0.99
1.00
2.02
1.04
1.02
1.02
1.02
1.01
1.07
2.98
1.03
157.66
157.14
149.59
145.60
138.28
136.33
128.25
121.79
117.59
66.78
56.80
45.11
41.60
30.23
23.75

(2*S*,4*R*,5*R*)-2-(6-methylpyridin-2-yl)-1-((4-nitrophenyl)sulfonyl)-5-vinylpiperidin-4-ol (*anti*-3.5o)



According to general procedure with *anti*-**3.4o** (21.0 mg, 0.05 mmol, 100 mol%), triphenylphosphine (39.4 mg, 0.15 mmol, 300 mol%, two portions) and DIAD (30.4 mg, 0.15 mmol, 300 mol%, two portions), the product *anti*-**3.5o** was obtained as gel in 65% yields (13.1 mg, 0.033 mmol) after flash chromatography (SiO_2: hexane/ethyl acetate, 5:1-2:1).

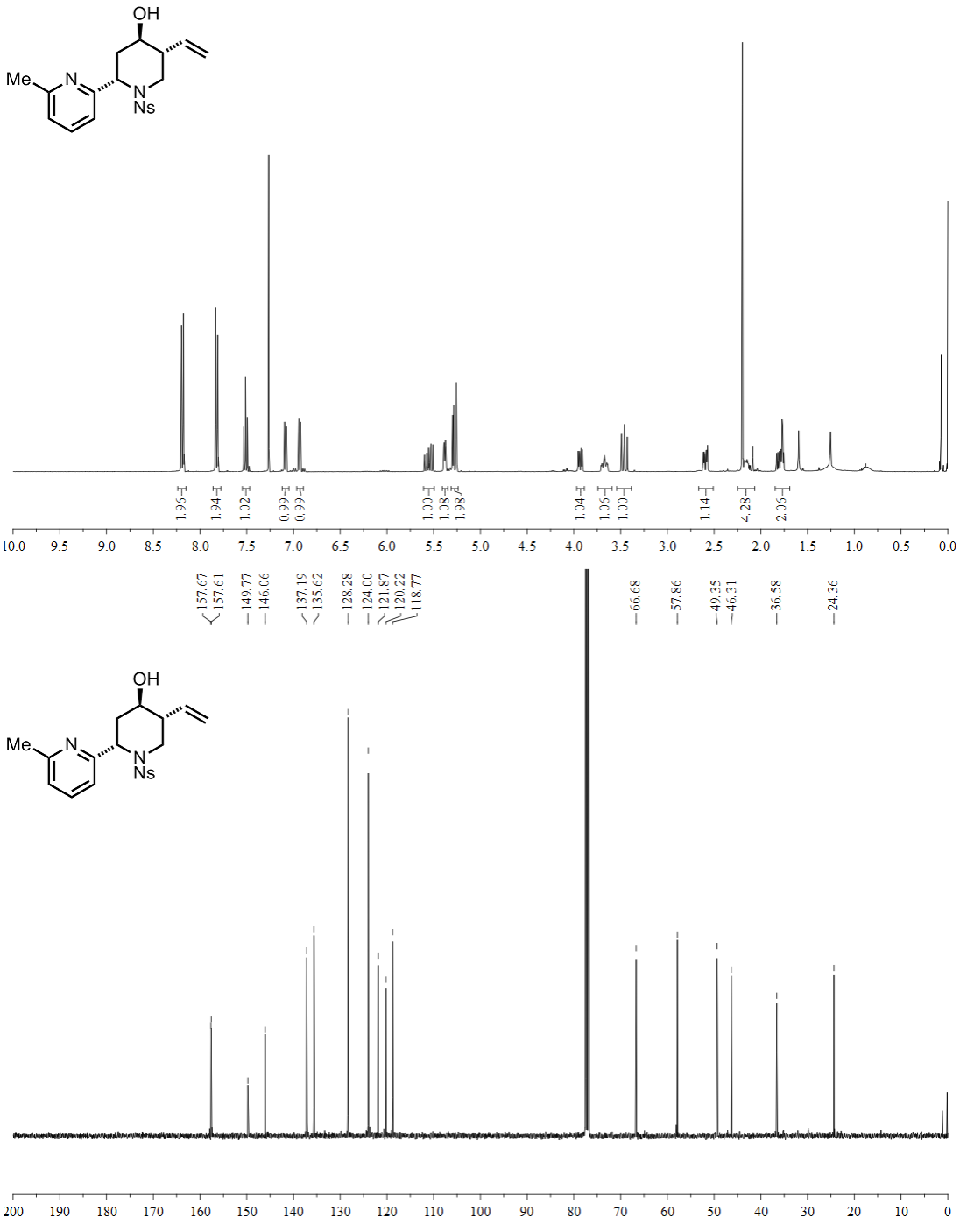
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.9 Hz, 2H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 5.55 (ddd, *J* = 17.5, 10.0, 8.6 Hz, 1H), 5.38 (d, *J* = 6.0 Hz, 1H), 5.31–5.24 (m, 2H), 3.93 (ddd, *J* = 12.9, 4.9, 1.1 Hz, 1H), 3.72–3.63 (m, 1H), 3.50–3.41 (m, 1H), 2.59 (ddd, *J* = 13.0, 4.3, 2.1 Hz, 1H), 2.20 (s, 3H), 2.18–2.10 (m, 1H), 1.85–1.73 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 157.6, 149.8, 146.1, 137.2, 135.6, 128.3, 124.0, 121.9, 120.2, 118.8, 66.7, 57.9, 49.4, 46.3, 36.6, 24.4.

LRMS (ESI) Calcd. for $C_{19}H_{21}N_3O_5SNa$ $[M+Na]^+$: 426.1, Found: 426.1.

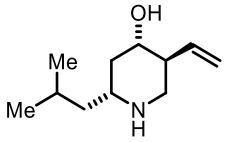
FTIR (neat): 2923, 2856, 1590, 1529, 1456, 1349, 1165, 1042, 992, 855 cm^{-1}.

$[\alpha]^{20}_D$ = -76.00 ° (c 1.00, $CHCl_3$).


OH
Me
N
N
Ns
1.96
1.94
1.02
0.99
0.99
1.00
1.08
1.98
1.04
1.06
1.00
1.14
4.28
2.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
157.67
157.61
149.77
146.06
137.19
135.62
128.28
124.00
121.87
120.22
118.77
66.68
57.86
49.35
46.31
36.58
24.36
OH
Me
N
N
Ns
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Deprotection of *syn*-5n to Form free Piperidine (*syn*-3.6n)

(2*R*,4*S*,5*S*)-2-isobutyl-5-vinylpiperidin-4-ol (*syn*-3.6n)



A flame-dried pressure tube equipped with a magnetic stir bar was charged *syn*-**3.5n** (18.4 mg, 0.05 mmol, 100 mol%) and K_2CO_3 (41.5 mg, 0.3 mmol, 600 mol%). The reaction tube was placed under an atmosphere of argon, PhSH (22 mg, 0.2 mmol, 400 mol%) and MeCN (0.5 mL, 0.1 M) was added by syringe. The tube was capped and the reaction mixture was allowed to stir at 50 ºC for 24 h. The reaction mixture was concentrated *in vacuo*. The product *syn*-**3.6n** was obtained as white solid in 85% yields (7.8 mg, 0.043 mmol) after flash chromatography (SiO_2: dichloromethane/methanol, 20:1-10:1).

^{1}H NMR (400 MHz, CD_3OD) δ 5.82–5.70 (m, 1H), 5.26–5.22 (m, 1H), 5.20 (d, *J* = 0.5 Hz, 1H), 3.58–3.50 (m, 1H), 3.21 (dd, *J* = 12.9, 4.5 Hz, 1H), 3.17–3.10 (m, 1H), 2.84 (t, *J* = 12.6 Hz, 1H), 2.25 (ddd, *J* = 7.8, 6.1, 3.3 Hz, 1H), 2.19 (ddd, *J* = 13.6, 4.5, 2.8 Hz, 1H), 1.75 (dp, *J* = 19.9, 6.6 Hz, 1H), 1.54–1.39 (m, 2H), 1.38–1.25 (m, 1H), 0.96 (dd, *J* = 8.0, 6.6 Hz, 6H).

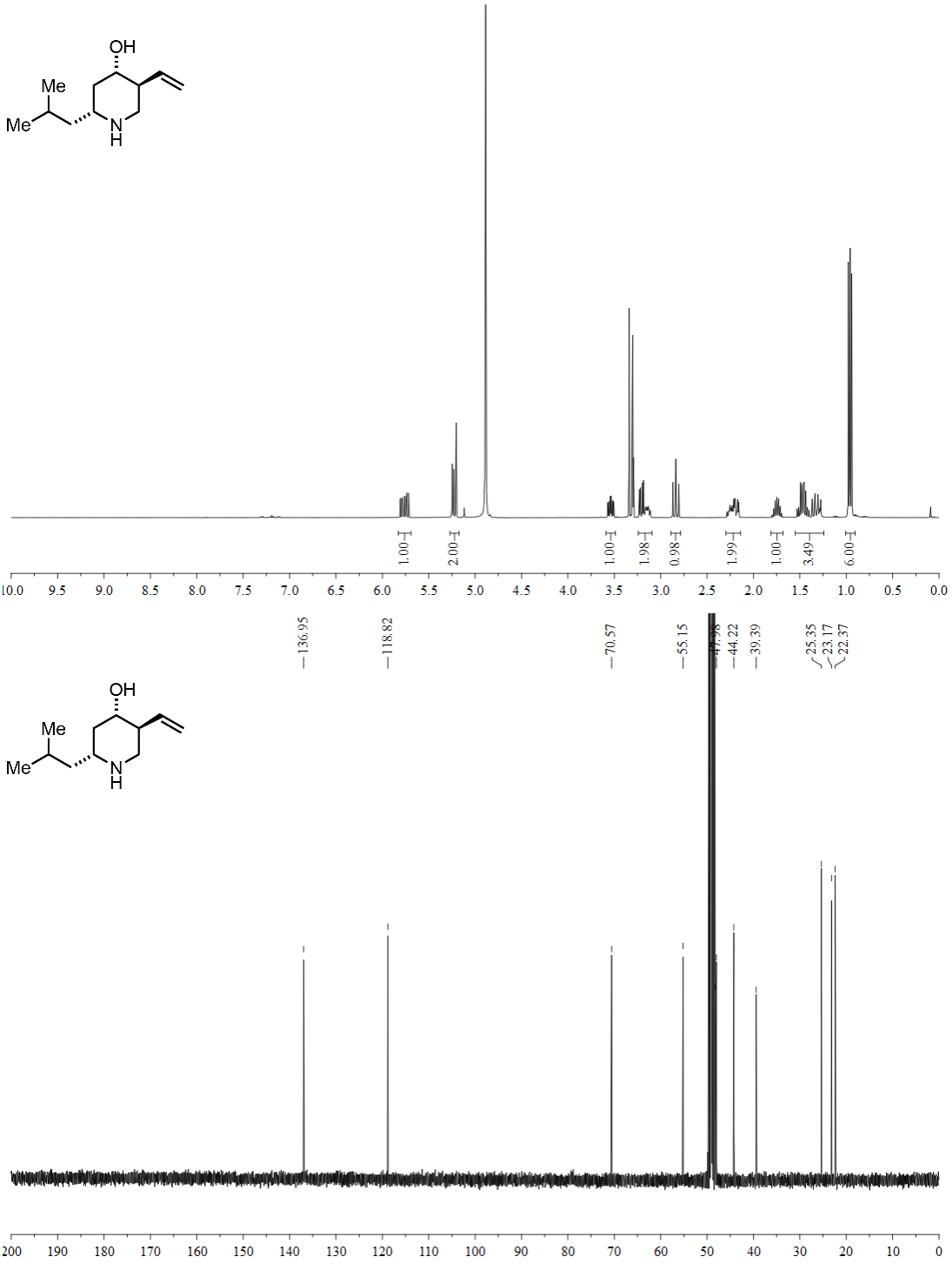
^{13}C NMR (100 MHz, CD_3OD) δ 136.9, 118.9, 70.6, 55.2, 48.3, 47.9, 44.2, 39.4, 25.4, 23.12, 22.4.

mp: 218-220 ºC.

LRMS (ESI) Calcd. for $C_{11}H_{21}NONa$ $[M+Na]^+$: 206.2, Found: 206.2.

FTIR (neat): 3399, 2956, 2924, 2851, 2359, 1443, 1260, 1024, 996, 801 cm^{-1}.

$[\alpha]^{20}_D$ = -11.19 ° (c 0.58, MeOH).


OH
Me
Me
N
H
1.00
2.00
1.00
1.98
0.98
1.99
1.00
3.49
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
136.95
118.82
70.57
55.15
47.98
44.22
39.39
25.35
23.17
22.37
OH
Me
Me
N
H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

X-ray Experimental for complex 3.4b–$CHCl_3$:

Crystals grew as colorless plates by slow evaporation from chloroform. The data crystal was cut from a larger crystal and had approximate dimensions; 0.22 x 0.15 x 0.03 mm. The data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a μ-focus Cu Kα radiation source (λ=1.5418Å) with collimating mirror monochromators. A total of 1665 frames of data were collected using-scans with a scan range of 1° and a counting time of 7.5 seconds per frame with a detector offset of +/- 40.5° and 20 seconds per frame with a detector offset of +/- 111°. The data were collected at 100 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data collection, unit cell refinement and data reduction were performed using Agilent Technologies CrysAlisPro V 1.171.37.31. The structure was solved by direct methods using SIR97 and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2013. Structure analysis was aided by use of the programs PLATON98 and WinGX. The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atoms bound to N2 and O5 were observed in a ΔF map and refined with isotropic displacement parameters.

A molecule of chloroform was disordered by rotation about one of the Cl to C bonds. The disorder was modeled by assigning the variable x to the site occupancy of one component of the disorder. The variable (1-x) was assigned to the site occupancy of the alternate component. The variable x was refined while restraining the geometry of the two components to be equivalent. A common isotropic displacement parameter was refined while refining x. In this way, the site occupancy for the major component of the disorder refined to 70(2)%. The chlorine atoms involved in the disorder were refined with

anisotropic displacement parameters that were restrained to be approximately isotropic in the final refinement model.

The absolute configuration was determined by the method of Flack. The Flack x parameter refined to 0.01(2). This assignment was corroborated by use of the Hooft y-parameter. The Hooft y-parameter refined to 0.011(7).

The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[((F_o))^2 + (0.0606*P)^2 + (0.4875*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.104, with R(F) equal to 0.0388 and a goodness of fit, S, = 1.03. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below. The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992). All figures were generated using SHELXTL/PC. Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 3.6 Crystal data and structure refinement for **3.4b-**$CHCl_3$.

Empirical formula	C19 H21 Cl3 N2 O5 S	
Formula weight	495.79	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 5.34030(10) Å	= 90°.
	b = 12.4724(2) Å	= 91.564(2)°.
	c = 17.1880(3) Å	= 90°.
Volume	1144.40(3) $Å^3$	
Z	2	
Density (calculated)	1.439 Mg/m^3	
Absorption coefficient	4.767 mm^{-1}	
F(000)	512	
Crystal size	0.220 x 0.150 x 0.027 mm	
Theta range for data collection	2.572 to 76.118°.	
Index ranges	-6<=h<=6, -15<=k<=15, -21<=l<=21	
Reflections collected	11741	
Independent reflections	4566 [R(int) = 0.0313]	
Completeness to theta = 67.684°	99.8 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.939 and 0.696	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4566 / 55 / 299	

Table 3.6 (cont'd)

Goodness-of-fit on F^2	1.023
Final R indices [I>2sigma(I)]	R1 = 0.0388, wR2 = 0.1025
R indices (all data)	R1 = 0.0400, wR2 = 0.1040
Absolute structure parameter	0.01(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.504 and -0.389 e.$Å^{-3}$

Table 3.7 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **3.4b-**$CHCl_3$. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	8313(6)	6272(3)	7124(2)	21(1)
C2	7783(7)	5680(3)	7778(2)	34(1)
C3	6000(9)	6064(4)	8286(2)	42(1)
C4	4859(7)	7024(3)	8122(2)	34(1)
C5	5368(8)	7623(3)	7475(2)	36(1)
C6	7114(7)	7238(3)	6962(2)	30(1)
C7	7236(6)	4184(3)	6024(2)	20(1)
C8	6671(5)	3450(2)	5324(2)	18(1)
C9	5714(6)	4099(3)	4639(2)	22(1)
C10	6971(7)	4266(3)	4000(2)	29(1)
C11	4742(6)	2597(3)	5547(2)	19(1)

Table 3.7 (cont'd)

C12	5454(6)	1982(3)	6282(2)	21(1)
C13	7548(6)	1318(3)	6319(2)	25(1)
C14	8128(6)	756(3)	7005(2)	31(1)
C15	6680(7)	849(3)	7658(2)	33(1)
C16	4616(7)	1524(3)	7618(2)	33(1)
C17	4025(6)	2094(3)	6939(2)	26(1)
C18	7292(10)	229(4)	8397(3)	48(1)
N1	2943(8)	7416(4)	8654(2)	50(1)
N2	8775(5)	5104(2)	5782(2)	20(1)
O1	2457(9)	6877(4)	9214(3)	76(1)
O2	1914(9)	8257(4)	8513(3)	81(1)
O3	11914(4)	4960(2)	6857(2)	29(1)
O4	11564(5)	6616(2)	6057(2)	29(1)
O5	4264(5)	1877(2)	4908(1)	24(1)
S1	10409(1)	5727(1)	6446(1)	20(1)
C19	10387(10)	3370(5)	9579(3)	56(1)
Cl1	9115(3)	2957(1)	8682(1)	59(1)
Cl2	11142(5)	4673(2)	9564(1)	74(1)
Cl3	13102(4)	2537(2)	9794(1)	68(1)
Cl2A	8880(10)	4797(4)	9843(3)	63(1)
Cl3A	13597(11)	3787(8)	9673(5)	107(3)

Table 3.8 Bond lengths [Å] and angles [°] for **3.4b**-$CHCl_3$.

C1-C2	1.381(5)	C11-C12	1.518(4)
C1-C6	1.389(5)	C11-H11	1.00
C1-S1	1.773(3)	C12-C17	1.387(5)
C2-C3	1.393(6)	C12-C13	1.392(5)
C2-H2	0.95	C13-C14	1.398(5)
C3-C4	1.369(6)	C13-H13	0.95
C3-H3	0.95	C14-C15	1.384(5)
C4-C5	1.374(6)	C14-H14	0.95
C4-N1	1.475(5)	C15-C16	1.387(6)
C5-C6	1.386(5)	C15-C18	1.516(5)
C5-H5	0.95	C16-C17	1.395(5)
C6-H6	0.95	C16-H16	0.95
C7-N2	1.478(4)	C17-H17	0.95
C7-C8	1.535(4)	C18-H18A	0.98
C7-H7A	0.99	C18-H18B	0.98
C7-H7B	0.99	C18-H18C	0.98
C8-C9	1.507(4)	N1-O1	1.207(6)
C8-C11	1.536(4)	N1-O2	1.205(6)
C8-H8	1.00	N2-S1	1.616(3)
C9-C10	1.320(5)	N2-H2N	0.96(5)
C9-H9	0.95	O3-S1	1.424(3)
C10-H10A	0.95	O4-S1	1.442(2)
C10-H10B	0.95	O5-H5O	0.72(4)
C11-O5	1.437(4)	C19-Cl2	1.675(6)

Table 3.8 (cont'd)

C19-Cl1	1.744(5)	C1-C6-H6	120.4
C19-Cl3A	1.795(8)	N2-C7-C8	109.9(2)
C19-Cl3	1.813(6)	N2-C7-H7A	109.7
C19-Cl2A	2.011(8)	C8-C7-H7A	109.7
C19-H19A	0.96	N2-C7-H7B	109.7
C19-H19B	0.96	C8-C7-H7B	109.7
C2-C1-C6	121.5(3)	H7A-C7-H7B	108.2
C2-C1-S1	118.5(3)	C9-C8-C7	110.3(2)
C6-C1-S1	119.8(3)	C9-C8-C11	110.6(2)
C1-C2-C3	119.0(4)	C7-C8-C11	109.7(2)
C1-C2-H2	120.5	C9-C8-H8	108.7
C3-C2-H2	120.5	C7-C8-H8	108.7
C4-C3-C2	118.7(4)	C11-C8-H8	108.7
C4-C3-H3	120.7	C10-C9-C8	124.5(3)
C2-C3-H3	120.7	C10-C9-H9	117.8
C3-C4-C5	123.1(4)	C8-C9-H9	117.8
C3-C4-N1	118.4(4)	C9-C10-H10A	120.0
C5-C4-N1	118.5(4)	C9-C10-H10B	120.0
C4-C5-C6	118.5(4)	H10A-C10-H10B	120.0
C4-C5-H5	120.8	O5-C11-C12	110.9(3)
C6-C5-H5	120.8	O5-C11-C8	110.4(2)
C5-C6-C1	119.2(4)	C12-C11-C8	113.7(2)
C5-C6-H6	120.4	O5-C11-H11	107.1

Table 3.8 (cont'd)

C12-C11-H11	107.1	H18A-C18-H18C	109.5
C8-C11-H11	107.2	H18B-C18-H18C	109.5
C17-C12-C13	118.8(3)	O1-N1-O2	122.5(4)
C17-C12-C11	119.7(3)	O1-N1-C4	118.5(5)
C13-C12-C11	121.4(3)	O2-N1-C4	119.0(5)
C12-C13-C14	119.7(3)	C7-N2-S1	117.9(2)
C12-C13-H13	120.1	C7-N2-H2N	114(3)
C14-C13-H13	120.1	S1-N2-H2N	111(3)
C15-C14-C13	121.7(3)	C11-O5-H5O	113(3)
C15-C14-H14	119.2	O3-S1-O4	120.22(16)
C13-C14-H14	119.2	O3-S1-N2	108.25(15)
C14-C15-C16	118.1(3)	O4-S1-N2	105.79(14)
C14-C15-C18	121.6(4)	O3-S1-C1	106.85(16)
C16-C15-C18	120.3(4)	O4-S1-C1	107.19(15)
C15-C16-C17	120.8(3)	N2-S1-C1	108.05(14)
C15-C16-H16	119.6	Cl2-C19-Cl1	111.2(3)
C17-C16-H16	119.6	Cl1-C19-Cl3A	120.9(4)
C12-C17-C16	120.8(3)	Cl2-C19-Cl3	111.5(3)
C12-C17-H17	119.6	Cl1-C19-Cl3	107.5(3)
C16-C17-H17	119.6	Cl1-C19-Cl2A	108.2(3)
C15-C18-H18A	109.5	Cl3A-C19-Cl2A	96.3(4)
C15-C18-H18B	109.5	Cl2-C19-H19A	108.8
H18A-C18-H18B	109.5	Cl1-C19-H19A	108.9
C15-C18-H18C	109. 5	Cl3-C19-H19A	108.8

Table 3.8 (cont'd)

Cl1-C19-H19B	110.2
Cl3A-C19-H19B	110.1
Cl2A-C19-H19B	110.1

Table 3.9 Anisotropic displacement parameters ($Å^2x10^3$) for **3.4b**-$CHCl_3$. The anisotropic displacement factor exponent takes the form: $-2^2[h^2a^{*2}U^{11}+...+2\ h\ k\ a^*\ b^*\ U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	19(1)	21(2)	24(1)	-5(1)	-3(1)	-4(1)
C2	44(2)	25(2)	33(2)	2(2)	10(1)	4(2)
C3	56(3)	35(2)	37(2)	-1(2)	18(2)	0(2)
C4	29(2)	37(2)	37(2)	-16(2)	6(2)	-5(2)
C5	40(2)	32(2)	36(2)	-9(2)	-5(2)	13(2)
C6	36(2)	28(2)	27(2)	-3(1)	-2(1)	7(1)
C7	22(1)	16(1)	24(1)	-2(1)	2(1)	-3(1)
C8	15(1)	14(1)	24(1)	-2(1)	0(1)	0(1)
C9	22(1)	13(1)	30(2)	-2(1)	-3(1)	-1(1)
C10	36(2)	22(2)	30(2)	2(1)	1(1)	4(1)
C11	18(1)	17(2)	23(1)	-3(1)	-1(1)	-1(1)
C12	18(1)	18(2)	26(1)	-1(1)	-3(1)	-4(1)
C13	20(2)	23(2)	33(2)	-1(1)	1(1)	-1(1)
C14	27(2)	23(2)	42(2)	3(2)	-8(1)	4(2)
C15	40(2)	28(2)	31(2)	4(1)	-8(1)	-4(2)
C16	37(2)	35(2)	28(2)	1(1)	4(1)	1(2)
C17	22(2)	26(2)	29(2)	-1(1)	1(1)	3(1)
C18	61(3)	42(2)	38(2)	12(2)	-14(2)	3(2)

Table 3.9 (cont'd)

N1	43(2)	55(3)	54(2)	-27(2)	12(2)	-3(2)
N2	20(1)	15(1)	24(1)	-1(1)	-1(1)	-2(1)
O1	93(3)	56(2)	83(3)	-17(2)	59(3)	-13(2)
O2	81(3)	93(4)	70(3)	-16(2)	21(2)	48(3)
O3	17(1)	33(1)	37(1)	-2(1)	-4(1)	6(1)
O4	28(1)	25(1)	35(1)	-2(1)	4(1)	-12(1)
O5	27(1)	20(1)	24(1)	-5(1)	2(1)	-7(1)
S1	15(1)	19(1)	26(1)	-2(1)	-1(1)	-2(1)
C19	51(3)	77(4)	41(2)	16(2)	0(2)	-14(3)
Cl1	68(1)	46(1)	64(1)	2(1)	-11(1)	-5(1)
Cl2	121(2)	54(1)	46(1)	-6(1)	-17(1)	-25(1)
Cl3	49(1)	104(2)	50(1)	15(1)	-4(1)	6(1)
Cl2A	76(3)	57(3)	55(2)	-5(2)	-22(2)	2(2)
Cl3A	51(3)	148(7)	122(5)	46(5)	14(3)	14(3)

Table 3.10 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **3.4b**-$CHCl_3$.

	x	y	z	U(eq)
H2	8622	5022	7881	40
H3	5585	5667	8736	51
H5	4541	8287	7380	43
H6	7487	7630	6506	36
H7A	5647	4447	6239	24
H7B	8144	3775	6437	24
H8	8253	3082	5178	21
H9	4095	4409	4670	26
H10A	8596	3967	3950	35
H10B	6252	4684	3590	35
H11	3138	2980	5646	23
H13	8579	1246	5881	30
H14	9552	300	7024	37
H16	3592	1599	8058	40
H17	2626	2565	6927	31
H18A	6922	-532	8313	72
H18B	6278	503	8820	72
H18C	9073	316	8535	72
H19A	9172	3255	9972	68
H19B	10020	2853	9974	68

Table 3.10 (cont'd)

H5O	5350(80)	1780(30)	4680(20)	13(10)
H2N	7880(80)	5600(40)	5450(30)	35(11)

Table 3.11 Torsion angles [°] for **3.4b**-$CHCl_3$.

C6-C1-C2-C3	0.1(6)	C11-C12-C13-C14	-179.4(3)
S1-C1-C2-C3	-175.3(3)	C12-C13-C14-C15	-0.6(5)
C1-C2-C3-C4	-0.9(6)	C13-C14-C15-C16	-0.2(6)
C2-C3-C4-C5	0.8(7)	C13-C14-C15-C18	179.2(4)
C2-C3-C4-N1	179.0(4)	C14-C15-C16-C17	-0.2(6)
C3-C4-C5-C6	0.1(6)	C18-C15-C16-C17	-179.6(4)
N1-C4-C5-C6	-178.1(3)	C13-C12-C17-C16	-2.3(5)
C4-C5-C6-C1	-0.9(6)	C11-C12-C17-C16	178.9(3)
C2-C1-C6-C5	0.8(5)	C15-C16-C17-C12	1.5(6)
S1-C1-C6-C5	176.2(3)	C3-C4-N1-O1	0.1(6)
N2-C7-C8-C9	-49.2(3)	C5-C4-N1-O1	178.4(4)
N2-C7-C8-C11	-171.2(2)	C3-C4-N1-O2	-179.5(5)
C7-C8-C9-C10	110.3(4)	C5-C4-N1-O2	-1.2(6)
C11-C8-C9-C10	-128.2(4)	C8-C7-N2-S1	-158.2(2)
C9-C8-C11-O5	60.4(3)	C7-N2-S1-O3	53.7(3)
C7-C8-C11-O5	-177.7(2)	C7-N2-S1-O4	-176.2(2)
C9-C8-C11-C12	-174.2(3)	C7-N2-S1-C1	-61.7(3)
C7-C8-C11-C12	-52.3(3)	C2-C1-S1-O3	-22.8(3)
O5-C11-C12-C17	-121.1(3)	C6-C1-S1-O3	161.7(3)
C8-C11-C12-C17	113.8(3)	C2-C1-S1-O4	-152.9(3)
O5-C11-C12-C13	60.1(4)	C6-C1-S1-O4	31.6(3)
C8-C11-C12-C13	-65.0(4)	C2-C1-S1-N2	93.5(3)
C17-C12-C13-C14	1.8(5)	C6-C1-S1-N2	-82.0(3)

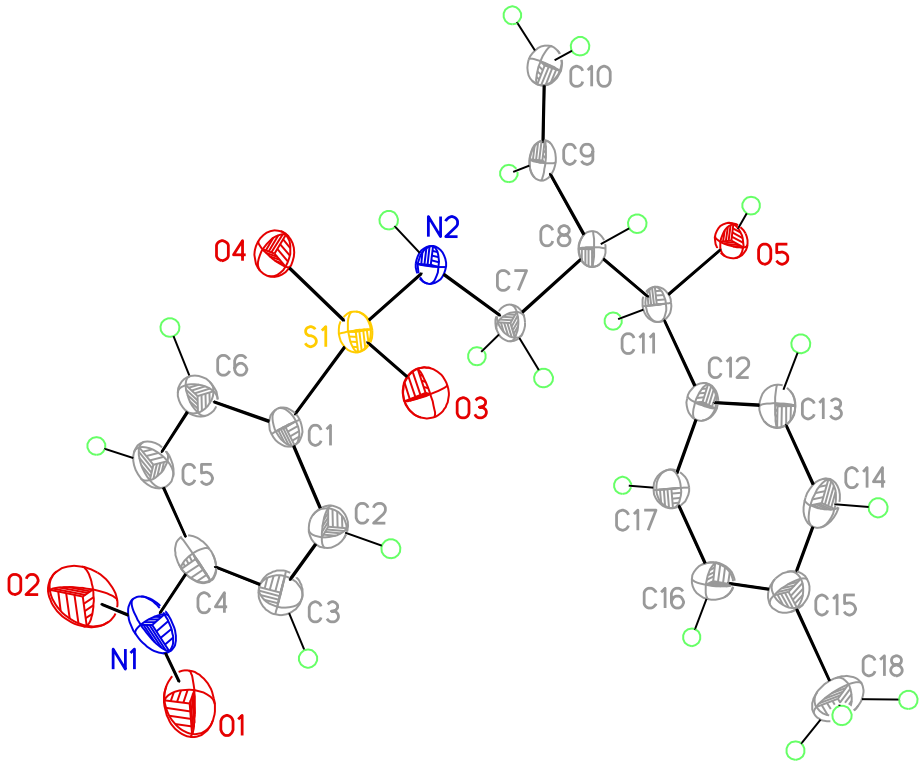
Table 3.12 Hydrogen bonds for **3.4b**-$CHCl_3$.

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O5-H5O...O4#1	0.72(4)	2.12(4)	2.832(4)	175(4)
N2-H2N...O5#2	0.96(5)	2.04(5)	2.971(3)	161(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y-1/2,-z+1 #2 -x+1,y+1/2,-z+1

Figure 3.1 View of **3.4b**-$CHCl_3$ showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



X-ray Experimental for complex *anti*-3.5m:

Table 3.13 Crystal data and structure refinement for *anti*-**3.5m**.

Empirical formula	C14 H18 N2 O5 S	
Formula weight	326.36	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.10640(10) Å	= 90°.
	b = 7.84280(10) Å	= 100.670(2)°.
	c = 12.2165(2) Å	= 90°.
Volume	763.258(19) $Å^3$	
Z	2	
Density (calculated)	1.420 Mg/m^3	
Absorption coefficient	2.124 mm^{-1}	
F(000)	344	
Crystal size	0.370 x 0.080 x 0.040 mm	
Theta range for data collection	3.682 to 76.003°.	
Index ranges	-9<=h<=10, -9<=k<=9, -15<=l<=15	
Reflections collected	8408	
Independent reflections	3059 [R(int) = 0.0189]	
Completeness to theta = 67.684°	100.0 %	
Absorption correction	Semi-empirical from equivalents	

Table 3.13 (cont'd)

Max. and min. transmission	1.00 and 0.805
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3059 / 1 / 205
Goodness-of-fit on F^2	1.053
Final R indices [I>2sigma(I)]	R1 = 0.0214, wR2 = 0.0559
R indices (all data)	R1 = 0.0215, wR2 = 0.0561
Absolute structure parameter	0.013(14)
Extinction coefficient	n/a
Largest diff. peak and hole	0.167 and -0.258 e.$Å^{-3}$

Table 3.14 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for *anti*-**3.5m**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	7232(2)	5833(2)	9067(2)	19(1)
C2	6023(2)	7278(2)	9214(2)	20(1)
C3	5305(2)	8197(2)	8131(2)	21(1)
C4	6696(2)	8893(2)	7563(2)	18(1)
C5	7893(2)	7429(2)	7418(1)	18(1)
C6	6368(3)	4279(3)	8460(2)	26(1)
C7	6001(3)	9636(3)	6436(2)	25(1)
C8	6433(3)	11110(3)	6056(2)	31(1)
C9	10888(2)	4472(2)	7916(2)	16(1)
C10	10603(2)	2798(2)	8215(1)	17(1)
C11	10845(2)	1477(2)	7517(2)	17(1)
C12	11388(2)	1868(3)	6534(2)	17(1)
C13	11685(2)	3523(3)	6223(2)	19(1)
C14	11423(2)	4849(2)	6924(2)	18(1)
N1	8526(2)	6606(2)	8498(1)	17(1)
N2	11654(2)	460(2)	5791(1)	20(1)
O1	4302(2)	9610(2)	8342(1)	29(1)
O2	10791(2)	5461(2)	9931(1)	21(1)
O3	11431(2)	7578(2)	8556(1)	21(1)
O4	11279(2)	-993(2)	6038(1)	28(1)

Table 3.14 (cont'd)

O5	12236(2)	791(2)	4960(1)	28(1)
S1	10485(1)	6132(1)	8819(1)	15(1)

Table 3.15 Bond lengths [Å] and angles [°] for *anti*-**3.5m**.

C1-N1	1.490(2)	C9-C10	1.394(2)
C1-C6	1.528(3)	C9-S1	1.7749(18)
C1-C2	1.530(2)	C10-C11	1.379(3)
C1-H1	1.00	C10-H10	0.95
C2-C3	1.524(3)	C11-C12	1.388(2)
C2-H2A	0.99	C11-H11	0.95
C2-H2B	0.99	C12-C13	1.386(3)
C3-O1	1.426(2)	C12-N2	1.470(2)
C3-C4	1.530(3)	C13-C14	1.388(3)
C3-H3	1.00	C13-H13	0.95
C4-C7	1.504(2)	C14-H14	0.95
C4-C5	1.535(2)	N1-S1	1.6075(15)
C4-H4	1.00	N2-O5	1.224(2)
C5-N1	1.473(2)	N2-O4	1.232(2)
C5-H5A	0.99	O1-H1O	0.84(3)
C5-H5B	0.99	O2-S1	1.4353(13)
C6-H6A	0.98	O3-S1	1.4384(14)
C6-H6B	0.98	N1-C1-C6	113.39(15)
C6-H6C	0.98	N1-C1-C2	105.98(14)
C7-C8	1.318(3)	C6-C1-C2	113.67(16)
C7-H7	0.95	N1-C1-H1	107.8
C8-H8A	0.95	C6-C1-H1	107.8
C8-H8B	0.95	C2-C1-H1	107.8
C9-C14	1.393(2)	C3-C2-C1	113.46(15)

Table 3.15 (cont'd)

C3-C2-H2A	108.9	C1-C6-H6B	109.5
C1-C2-H2A	108.9	H6A-C6-H6B	109.5
C3-C2-H2B	108.9	C1-C6-H6C	109.5
C1-C2-H2B	108.9	H6A-C6-H6C	109.5
H2A-C2-H2B	107.7	H6B-C6-H6C	109.5
O1-C3-C2	110.49(16)	C8-C7-C4	125.71(19)
O1-C3-C4	107.29(15)	C8-C7-H7	117.1
C2-C3-C4	111.57(15)	C4-C7-H7	117.1
O1-C3-H3	109.1	C7-C8-H8A	120.0
C2-C3-H3	109.1	C7-C8-H8B	120.0
C4-C3-H3	109.1	H8A-C8-H8B	120.0
C7-C4-C3	111.77(15)	C14-C9-C10	121.41(17)
C7-C4-C5	108.76(15)	C14-C9-S1	120.55(14)
C3-C4-C5	108.68(15)	C10-C9-S1	118.02(14)
C7-C4-H4	109.2	C11-C10-C9	119.78(16)
C3-C4-H4	109.2	C11-C10-H10	120.1
C5-C4-H4	109.2	C9-C10-H10	120.1
N1-C5-C4	110.30(14)	C10-C11-C12	118.25(16)
N1-C5-H5A	109.6	C10-C11-H11	120.9
C4-C5-H5A	109.6	C12-C11-H11	120.9
N1-C5-H5B	109.6	C13-C12-C11	122.89(17)
C4-C5-H5B	109.6	C13-C12-N2	118.77(17)
H5A-C5-H5B	108.1	C11-C12-N2	118.34(16)
C1-C6-H6A	109.5	C12-C13-C14	118.59(17)

Table 3.15 (cont'd)

C12-C13-H13	120.7	O5-N2-C12	118.40(16)
C14-C13-H13	120.7	O4-N2-C12	118.19(16)
C13-C14-C9	119.08(17)	C3-O1-H1O	104(2)
C13-C14-H14	120.5	O2-S1-O3	119.67(8)
C9-C14-H14	120.5	O2-S1-N1	107.78(8)
C5-N1-C1	115.96(14)	O3-S1-N1	107.87(8)
C5-N1-S1	118.93(12)	O2-S1-C9	107.42(8)
C1-N1-S1	122.78(12)	O3-S1-C9	105.81(8)
O5-N2-O4	123.41(17)	N1-S1-C9	107.78(8)

Table 3.16 Anisotropic displacement parameters ($Å^2x10^3$) for *anti*-**3.5m**. The anisotropic displacement factor exponent takes the form: $-2^2[h^2a^{*2}U^{11}+...+2\ h\ k\ a^*\ b^*\ U^{12}]$.

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}	
C1	18(1)	19(1)	21(1)	2(1)	8(1)	0(1)
C2	16(1)	21(1)	26(1)	-2(1)	10(1)	-1(1)
C3	14(1)	17(1)	31(1)	-2(1)	5(1)	2(1)
C4	16(1)	16(1)	20(1)	-1(1)	2(1)	2(1)
C5	18(1)	18(1)	18(1)	0(1)	4(1)	2(1)
C6	25(1)	18(1)	36(1)	0(1)	9(1)	-2(1)
C7	23(1)	24(1)	25(1)	0(1)	-2(1)	5(1)
C8	35(1)	28(1)	29(1)	7(1)	0(1)	7(1)
C9	13(1)	17(1)	20(1)	1(1)	3(1)	3(1)
C10	16(1)	19(1)	18(1)	3(1)	6(1)	2(1)
C11	17(1)	14(1)	21(1)	3(1)	4(1)	1(1)
C12	16(1)	17(1)	18(1)	1(1)	2(1)	3(1)
C13	20(1)	20(1)	18(1)	4(1)	6(1)	2(1)
C14	19(1)	15(1)	21(1)	4(1)	6(1)	2(1)
N1	15(1)	18(1)	18(1)	2(1)	6(1)	2(1)
N2	22(1)	20(1)	18(1)	0(1)	3(1)	4(1)
O1	17(1)	21(1)	50(1)	-2(1)	13(1)	4(1)
O2	22(1)	22(1)	18(1)	-1(1)	2(1)	5(1)
O3	17(1)	17(1)	30(1)	-3(1)	7(1)	-1(1)
O4	41(1)	17(1)	28(1)	-2(1)	10(1)	-1(1)
O5	41(1)	27(1)	20(1)	0(1)	13(1)	5(1)
S1	14(1)	14(1)	18(1)	-1(1)	4(1)	2(1)

Table 3.17 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for *anti*-**3.5m**.

	x	y	z	U(eq)
H1	7803	5458	9825	23
H2A	5085	6803	9535	24
H2B	6620	8115	9752	24
H3	4595	7384	7616	25
H4	7332	9795	8044	21
H5A	7295	6578	6890	22
H5B	8848	7877	7104	22
H6A	5473	3887	8840	39
H6B	7191	3364	8461	39
H6C	5885	4589	7690	39
H7	5179	8985	5958	30
H8A	7251	11803	6506	38
H8B	5928	11480	5331	38
H10	10244	2568	8898	21
H11	10644	329	7704	21
H13	12059	3745	5544	23
H14	11607	5997	6729	22
H1O	3440(40)	9160(40)	8510(30)	53(9)

Table 3.18 Torsion angles [°] for *anti*-**3.5m**.

O1-C3-C4-C7	-64.93(19)	C2-C1-N1-S1	140.00(13)
C2-C3-C4-C7	173.92(15)	C13-C12-N2-O5	4.9(2)
O1-C3-C4-C5	175.03(15)	C11-C12-N2-O5	-175.34(16)
C2-C3-C4-C5	53.88(19)	C13-C12-N2-O4	-175.18(17)
C7-C4-C5-N1	-176.83(14)	C11-C12-N2-O4	4.6(2)
C3-C4-C5-N1	-54.94(18)	C5-N1-S1-O2	176.14(13)
C3-C4-C7-C8	133.9(2)	C1-N1-S1-O2	-21.90(16)
C5-C4-C7-C8	-106.1(2)	C5-N1-S1-O3	45.63(15)
C14-C9-C10-C11	-0.4(3)	C1-N1-S1-O3	-152.41(13)
S1-C9-C10-C11	177.74(13)	C5-N1-S1-C9	-68.20(15)
C9-C10-C11-C12	0.7(3)	C1-N1-S1-C9	93.77(15)
C10-C11-C12-C13	-0.5(3)	C14-C9-S1-O2	-151.51(14)
C10-C11-C12-N2	179.74(15)	C10-C9-S1-O2	30.38(16)
C11-C12-C13-C14	-0.1(3)	C14-C9-S1-O3	-22.60(16)
N2-C12-C13-C14	179.63(16)	C10-C9-S1-O3	159.29(14)
C12-C13-C14-C9	0.5(3)	C14-C9-S1-N1	92.59(15)
C10-C9-C14-C13	-0.3(3)	C10-C9-S1-N1	-85.52(15)
S1-C9-C14-C13	-178.32(14)		
C4-C5-N1-C1	60.42(19)		
C4-C5-N1-S1	-136.40(13)		
C6-C1-N1-C5	67.8(2)		
C2-C1-N1-C5	-57.54(18)		
C6-C1-N1-S1	-94.63(17)		

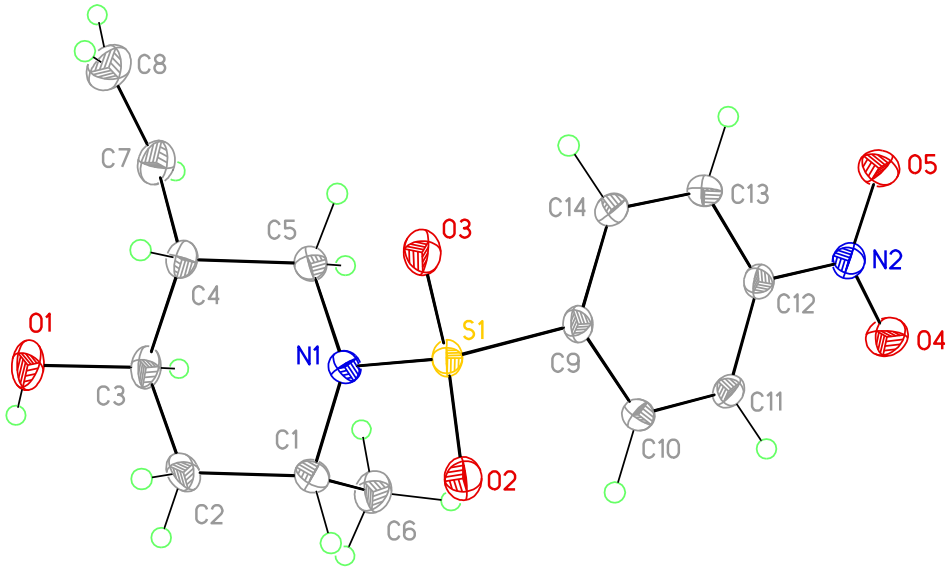
Table 3.19 Hydrogen bonds for *anti*-**3.5m** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O1-H1O...O3#1	0.84(3)	2.06(4)	2.872(2)	163(3)

Symmetry transformations used to generate equivalent atoms:

#1 x-1,y,z

Figure 3.2 View of *anti*-**3.5m** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



Chapter 4: Total Synthesis of (+)-SCH 351448: Efficiency via Chemoselectivity and Redox-Economy Powered by Metal Catalysis*

4.1 INTRODUCTION

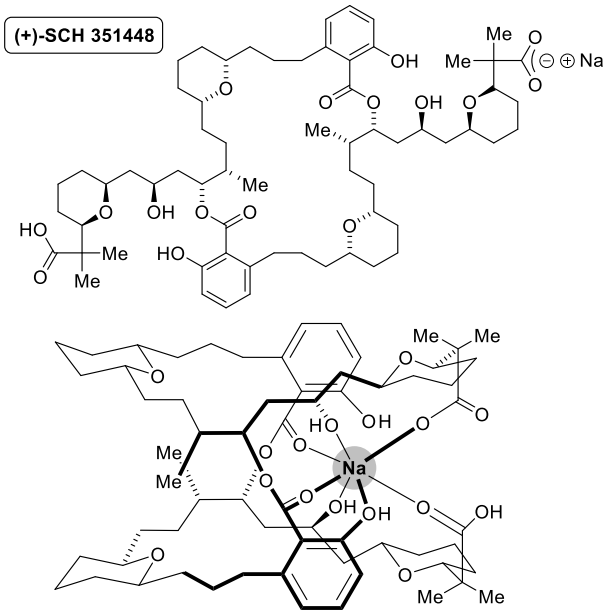
Chemoselectivity (site-selectivity),[1] the ability to discriminate between like or unlike functional groups, and redox-economy[2] have the greatest potential to impact step-economy, which may be considered the primary indicator of strategic efficiency[3] among the many issues of selectivity that impact chemical synthesis. In the syntheses of complex molecules, using protecting groups and discrete oxidation level adjustments, which could be precluded by chemoselective and redox-economic methods, may account for over half the total steps.[4-6] Taking advantages of these strategies, the Krische group has developed a lexicon of catalytic methods[7] for the direct stereo- and site-selective conversion of lower alcohols to higher alcohols, as well as related carbonyl reductive couplings mediated by 2-propanol.[7] These methods bypass discrete alcohol-to-carbonyl redox reactions and use of premetalated *C*-nucleophiles and have been shown to streamline the synthesis of diverse polyketide natural products.[7d]

The type I polyketide (+)-SCH 351448,[8,9] an ionophoric macrodiolide bearing 14 stereogenic centers, is an ideal vehicle to demonstrate the impact of redox-economy and chemoselectivity on synthetic efficiency, as eight elegant prior syntheses are available to serve as benchmarks (Figure 4.1).[10-12]

Previously, 22-32 steps (LLS) were required to construct (+)-SCH 351448.[10-12] Through the use of exclusive chemoselectivity (site-selective modification of one functional group in the presence of multiple like/unlike functional groups), inclusive chemoselectivity (concomitant modification of multiple like/unlike functional groups) and

* Adapted with the permission from (Wang, G.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 8088.). Copyright (2016) American Chemical Society.

redox-economic methods, (+)-SCH 351448, is now prepared in only 14 steps (LLS). An analysis of reaction type for past and present syntheses suggest the accumulation of chemoselective and redox-economic processes manifest in the present route as an increased proportion of skeletal construction events, an outcome that is better aligned with the ideals of synthetic efficiency.[13]



Total[b] or Formal[c] Syntheses	LLS (TS)	Skeletal Assembly	Redox Reactions	Protection-Deprotection	Other Reactions
Lee[b] (ref. 10a,b)	27 (46)	9 (33%)	8 (30%)	7 (26%)	3 (11%)
De Brabander[b] (ref. 10c,d)	22 (41)	7 (32%)	3 (14%)	9 (40%)	3 (14%)
Leighton[b] (ref. 10e)	25 (39)	12 (48%)	6 (24%)	6 (24%)	1 (4%)
Crimmins[b] (ref. 10f)	32 (54)	10 (31%)	7 (22%)	7 (22%)	8 (25%)
Loh[c] (ref. 11a)	23 (48)	10 (43%)	5 (22%)	8 (35%)	0
Rychnovsky[b] (ref. 10g)	24 (48)	6 (25%)	8 (33%)	9 (38%)	1 (4%)
Panek[b] (ref. 10h)	26 (48)	8 (31%)	7 (27%)	9 (34%)	2 (8%)
Hong[c] (ref. 11b)	28 (68)	9 (32%)	6 (21%)	10 (36%)	3 (11%)
Krische[b] (*This Work*)	14 (22)	8 (57%)	3 (21.5%)	3 (21.5%)	0

[a]For graphical summaries of prior total syntheses, see Supporting Infor-mation. Longest Linear Sequence (LLS); Total Steps (TS). Only transfor-mations in the longest linear sequence (LLS) are considered in the analysis of reaction type.

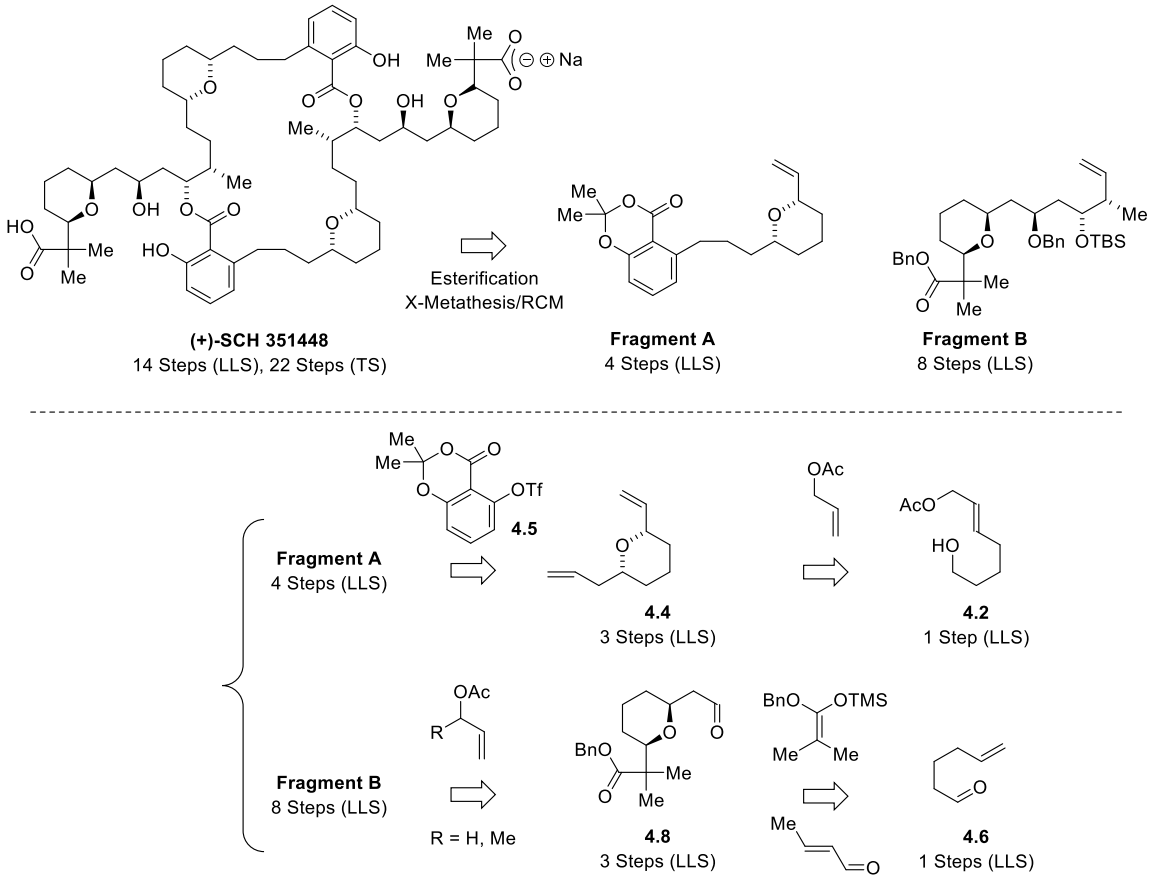
Figure 4.1 The type I polyketide (+)-SCH 351448, depiction of the sodium ion binding motif adapted from single crystal X-ray diffraction data and summary of synthetic work.[a]

(+)-SCH 351448, a secondary metabolite of *Micromonospora* sp. bacteria, was identified in connection with a bioassay-guided fractionation aimed at the identification of cholesterol reducing agents.[8] Specifically, (+)-SCH 351448 is a selective activator of low density lipoprotein receptor (LDL-R) promoter ($IC_{50} = 25$ μM). As increased expression of LDL-R decreases blood serum cholesterol levels,[14] (+)-SCH 351448, the first small molecule activator of the LDL-R promoter, has garnered interest from synthetic chemists as a potential starting point for the design of therapeutic agents for the treatment of hypercholesterolemia.[10-12]

4.2 Retrosynthetic Analysis

The following retrosynthetic analysis of (+)-SCH 351448 was envisioned (Scheme 4.1). The symmetric macrodiolide is assembled from Fragments **A** and **B** via esterification and cross-metathesis/RCM reactions.[15] For the synthesis of Fragment **A**, 4 consecutive metal catalyzed reactions are employed: cross-metathesis to form alcohol **4.2**,[15,18] tandem nucleophilic[16a,b] and electrophilic[17] allylations to convert alcohol **4.2** to pyran **4.4**[18] and the Suzuki cross-coupling of pyran **4.4** with aryl triflate **4.5**.[19] Fragment **B** is prepared in 8 steps from 5-hexen-1-ol **4.1**. Key transformations include Kiyooka's variant of the enantioselective Mukaiyama aldol reaction (applied to aldehyde **4.6**)[20] followed by Fuwa's cascading cross-metathesis-*oxa*-Michael cyclization[21,22] to form pyran **4.8**, with upon sequential asymmetric transfer hydrogenative allylation[16a,b] and crotylation[16c,d] deliver to Fragment **B**. The proposed synthesis of (+)-SCH 351448 depends on the implementation of several chemoselective and redox-economic transformations. For example, the C-H allylation of alcohol **4.2** avoids discrete alcohol-to-carbonyl redox reactions and requires chemoselective ionization of allylic carboxylate groups. The hydroboration of pyran **4.4** requires discrimination between allylic *vs* homoallylic terminal olefin moieties. The two-

step conversion of aldehyde **4.6** to pyran **4.8** occurs in the absence of redox reactions, whereas the final step of the synthesis, the concomitant hydrogenation and hydrogenolysis of six functional groups (two olefins, two benzyl ethers, two benzyl esters), represents a redox event that embodies a high degree of inclusive chemoselectivity. Although the endgames differ, it should be noted that Fragments A and B appears as intermediates in total syntheses by Lee (4 vs 16 steps)[10a,b] and Panek (8 vs 18 steps),[10h] respectively.



Scheme 4.1 Retrosynthetic analysis of (+)-SCH 351448.

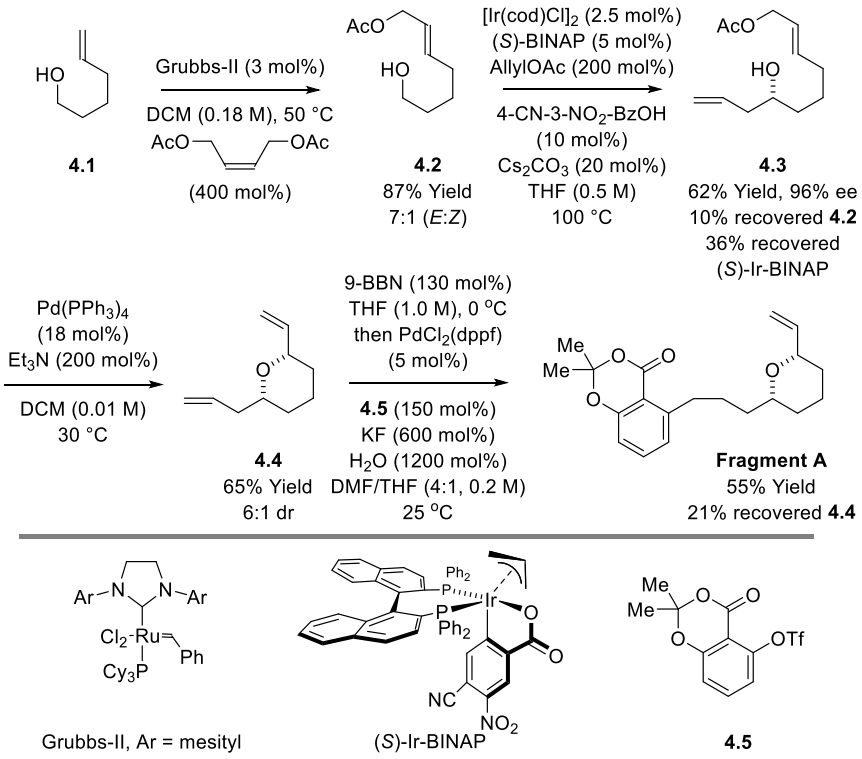
4.3 Synthesis of Fragment A.

The synthesis of Fragment **A** is achieved using 4 consecutive metal catalyzed transformations (Scheme 4.2). Cross-metathesis of 5-hexen-1-ol **4.1** with *cis*-1,4-diacetoxy-2-butene[18] using the second generation Grubbs catalyst[15,23] delivers the allylic acetate **4.2** in 87% yield as a 7:1 mixture of alkene *E*:*Z* stereoisomers. Transfer hydrogenative *C*-allylation of allylic acetate **4.2** using allyl acetate as the allyl donor provides the homoallylic alcohol **4.3** in 62% yield and 96% enantiomeric excess. Here, chemoselective activation of allylic acetates is achieved by virtue of the fact that the stability of late transition metal-olefin π-complex decreases with increasing degree of olefin substitution.[24] Tsuji-Trost cyclization[17] converts the homoallylic alcohol **4.3** to the 2,6-*cis*-disubstituted pyran **4.4** with good levels of diastereoselectivity, as determined by ^{1}H NMR analysis.[18] The Suzuki cross-coupling of pyran **4.4** with aryl triflate **4.5** requires chemoselective hydroboration of allylic *vs* homoallylic ethers. Due to the negative inductive effect of the pyran oxygen, the alkene moiety of the homoallylic ether undergoes selective hydroboration with 9-BBN, enabling formation of Fragment **A** in 55% yield, along with a 21% yield of recovered pyran **4.4**. Thus, Fragment **A**, previously made in 16 steps (LLS),[10a,b] is now made in four steps (LLS).

4.4 Synthesis of Fragment B.

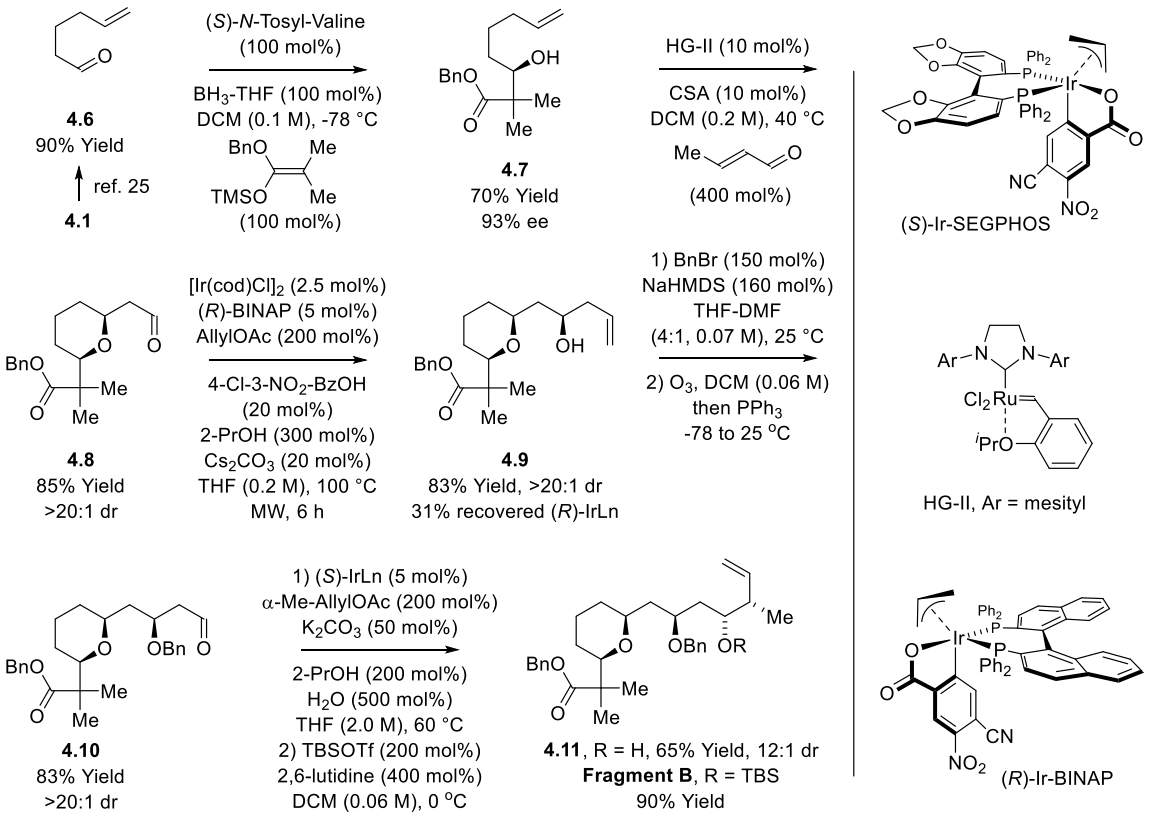
The synthesis of Fragment **B** begins with Moffatt-Swern oxidation of 5-pentenol **4.1** (Scheme 4.3).[25] The resulting aldehyde **4.6** is subjected to Kiyooka's variant of the enantioselective Mukaiyama aldol reaction[20] to furnish the neopentyl alcohol **4.7** in 70% yield and 93% *ee*. In alignment with Fuwa's observations,[21,22] cross-metathesis of unsaturated alcohol **4.7** with crotonaldehyde in the presence of substoichiometric quantities of (*S*)-camphorsulfonic acid using the second-generation Hoveyda-Grubbs catalyst occurs with spontaneous *oxa*-Michael cyclization to furnish the 2,6-disubstituted pyran **4.8** as a

single diastereomer, as determined by ^{1}H NMR analysis. Exposure of aldehyde **4.8** to conditions for allylation *via* 2-propanol mediated for transfer hydrogenation enabled formation of homoallylic alcohol **4.9**, which upon benzylation and ozonolysis delivered aldehyde **4.10**. Transfer hydrogenative crotylation of **4.10** provided the homoallylic alcohol **4.11** with good levels of *anti*-diastereoselectivity (12:1 *dr*) accompanied by complete levels of stereocontrol at the newly formed carbinol stereocenter. Conversion to the TBS ether completes the synthesis of Fragment **B** in a total of eight steps (LLS). Previously, Fragment **B** was prepared in 18 steps (LLS).[10h]



[a]Yields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary phase HPLC analysis. Identical yields and diastereoselectivities are observed upon use of recovered (S)-IrLn in the conversion of **4.2** to **4.3**.

Scheme 4.2 Synthesis of Fragment **A** using four consecutive metal catalyzed transformations.[a]



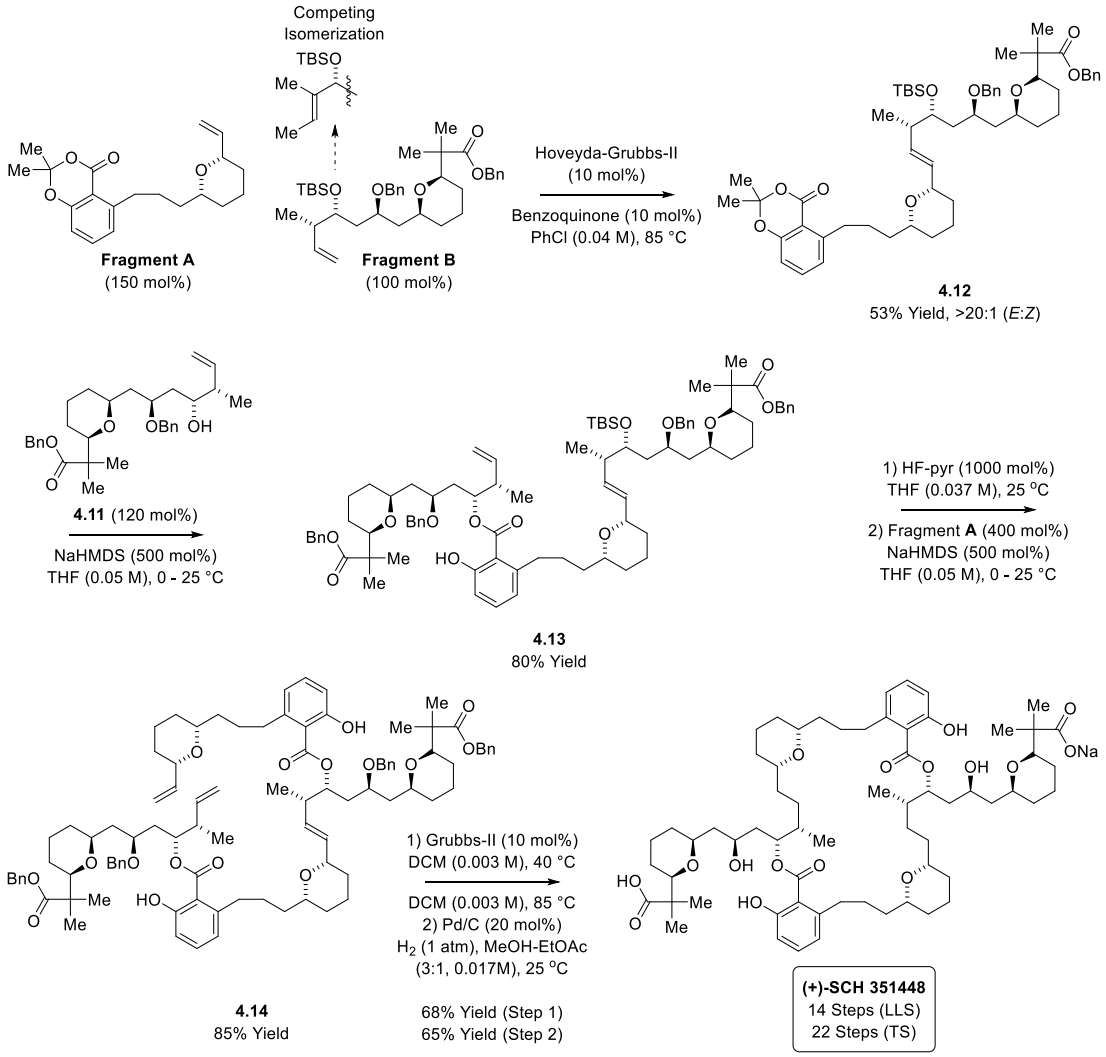
[a]Yields are of material isolated by silica gel chromatography. Enantiose-lectivity was determined by chiral stationary phase HPLC analysis. CSA refers to (S)-camphorsulfonic acid. Identical yields and diastereoselectivi-ties are observed upon use of recovered (R)-IrLn in the conversion of **4.8** to **4.9**.

Scheme 4.3 Synthesis of Fragment **B.**[a]

4.5 UNION OF FRAGMENTS A AND B AND TOTAL SYNTHESIS OF (+)-SCH 351448.

The assembly of Fragments **A** and **B** to form (+)-SCH 351448 is accomplished in a step-wise manner through successive esterification and cross-metathesis reactions (Scheme 4.4). Initial attempts at the cross-metathesis of Fragments **A** and **B** using conditions reported by Panek suffered from competing isomerization.[10h,26] Using the second generation Hoveyda-Grubbs catalyst in combination with 1,4-benzoquinone,[27] the desired product of cross-metathesis **4.12** could be formed in 53% yield. Exposure of compound **4.12** to the secondary alcohol **4.11** in the presence of sodium hexamethyldisilazide (NaHMDS) provided the product of transesterification **4.13** in 80%

yield. This transformation was very sensitive to moisture and optimal results required use of reactants dried through repeated evaporation from benzene. Removal of the TBS protecting group followed by a second transesterification provided compound **4.14** in 85% yield. Ring-closing metathesis followed by concomitant hydrogenation and hydrogenolysis of the two olefins, two benzyl ethers and two benzylic esters (inclusive chemoselectivity) provides (+)-SCH 351448 in 14 steps (LLS).[28]



[a]Yields are of material isolated by silica gel chromatography.

Scheme 4.4 Union of Fragments **A** and **B** and total synthesis of (+)-SCH 351448.[a]

4.6 CONCLUSION

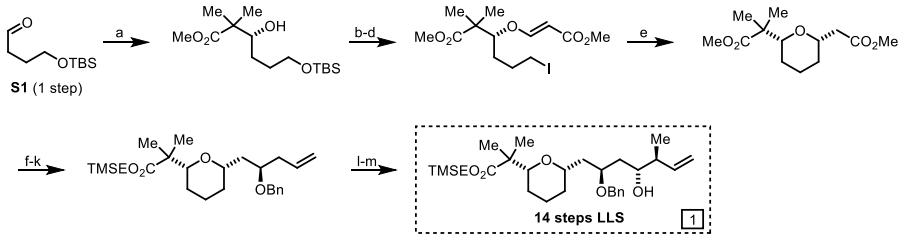
In summary, as the macrodiolide ionophore (+)-SCH 351448, a type I polyketide bearing 14 stereogenic centers, is prepared in 14 steps (LLS). In eight prior syntheses, 22−32 steps (LLS) were required. An analysis of reaction type across each route suggests enhanced efficiency may be attributed to the use of multiple chemoselective and redox-economic[2] functional group interconversions, a conclusion that adds clarity *vis-à-vis* strategy selection amid an ever-expanding and evolving lexicon of synthetic methods. Future studies will focus on the discovery, development, and application of catalytic methods for protecting-group-free skeletal assembly that merge redox and C−C bond construction events.[2]

4.7 EXPERIMENTAL DETAILS

Summaries of Previous Syntheses:

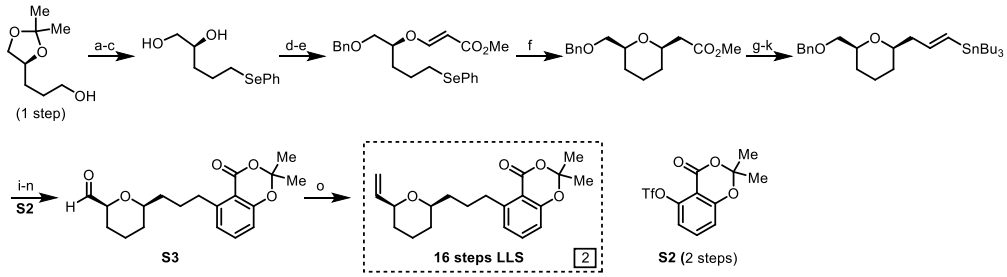
A. Lee *et al. J. Am. Chem. Soc.* **2004**, *126*, 2680.; *J. Org. Chem.* **2005**, *70*, 6321.

Fragment 1



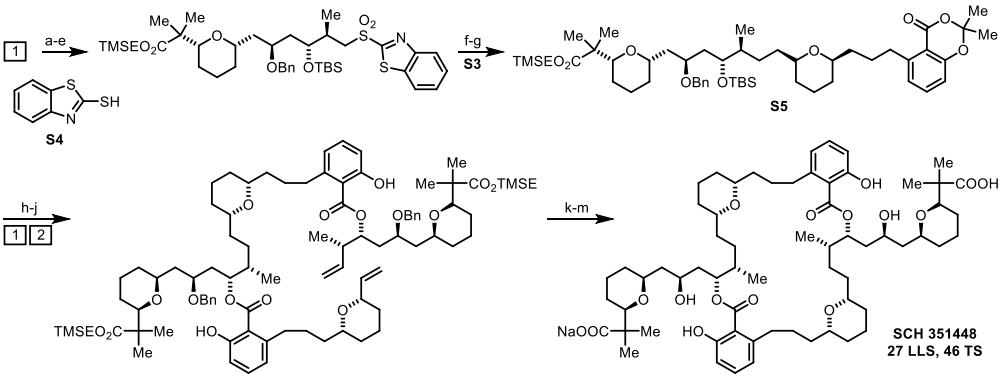
Key: (a) *N*-tosyl-(*S*)-valine, BH_3-THF, DCM; **S1**, $Me_2CC(OMe)(OTMS)$, -78°C; (b) $CHCCO_2Me$, NMM, MeCN; (c) concentrated HCl, MeOH; (d) I_2, Ph_3P, imidazole, THF, 0 °C; (e) H_3PO_2, 1-ethylpiperidine, Et_3B, EtOH; (f) KOH, THF-H_2O-MeOH (3:1:1); (g) BH_3-DMS, $B(OMe)_3$, THF, 0 °C; (h) SO_3-Pyr, TEA, DMSO-DCM (1:1), 0 °C; (i) $CH_2CHCH_2B(^{l}Ipc)_2$, ether, -78 °C; NaOH, H_2O_2, reflux; (j) NaHMDS, BnBr, THF-DMF (4:1), 0 °C to room temperature; (k) $Ti(O\textit{i}\text{-}Pr)_4$, $TMSCH_2CH_2OH$, DME, 120 °C; (l) OsO_4, NMO, acetone-H_2O (3:1); $NaIO_4$; (m) (*E*)-$CH_3CHCHCH_2B(^{d}Ipc)_2$,THF, -78 °C; NaOH, H_2O_2, -78 °C to room temperature.

Fragment 2



Key: (a) TsCl, TEA, DCM, 0 °C; (b) PhSeSePh, $NaBH_4$, EtOH; (c) concentrated HCl, MeOH; (d) Bu_2SnO, benzene, reflux (-H_2O); BnBr, TBAI, benzene, reflux; (e) $CHCCO_2Me$, NMM, MeCN; (f) *n*-Bu_3SnH, AIBN, benzene (0.01 M), reflux; (g) LAH, THF, 0 °C; (h) SO_3-Pyr, TEA, DMSO-DCM (1:1), 0 °C; (i) CBr_4, HMPT, THF, -30 °C; (j) *n*-BuLi, THF, -78 °C; (k) *n*-Bu_3SnH, AIBN, benzene (0.02 M), reflux; (l) $PdCl_2(PPh_3)_2$, **S2**, LiCl, Ph_3P, DMF (0.1 M), 120 °C; (m) H_2, Pd/C, MeOH; (n) SO_3-Pyr, TEA, DMSO-DCM (1:1), 0 °C; (o) Ph_3PCH_3+Br-, *n*-BuLi, THF, 0 °C; **S3**, -78 °C to room temperature.

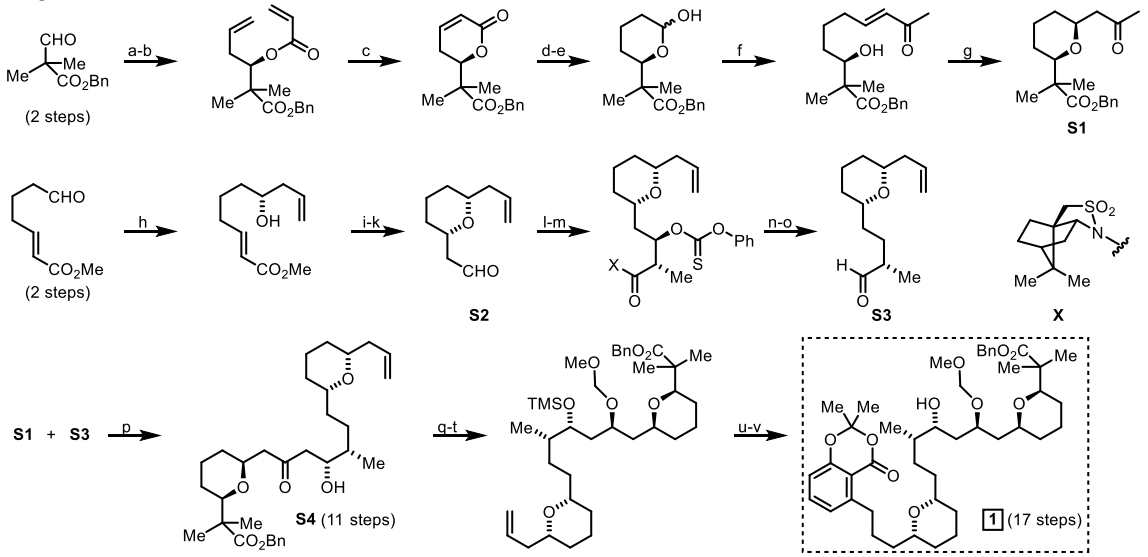
Fragment Union and End Game



Key: (a) TBSOTf, 2,6-lutidine, DCM, 0 °C; (b) OsO_4, NMO, acetone-H_2O(3:1); $NaIO_4$; (c) $NaBH_4$, EtOH; (d) **S4**, DIAD, Ph_3P, THF, 0 °C; (e) $(NH_4)_6Mo_7O_{24}$-$4H_2O$, H_2O_2, EtOH, 0 °C to room temperature; (f) NaHMDS, ether, -78 °C; **S3** (syringe pump, 30 min), -78 °C to room temperature; (g) TsNHNH_2, NaOAc, DME-H_2O (1:1), reflux; (h) NaHMDS, THF, 0 °C; **1**; (i) concentrated HCl, MeOH; (j) NaHMDS, THF, 0 °C; **2**, 0 °C; (k) 10 mol % Grubbs' catalyst (2nd generation), DCM (3 mM), 80 °C; (l) H_2, Pd/C, MeOH-EtOAc (3:1); (m) TBAF, THF; 4 N HCl (saturated with NaCl).

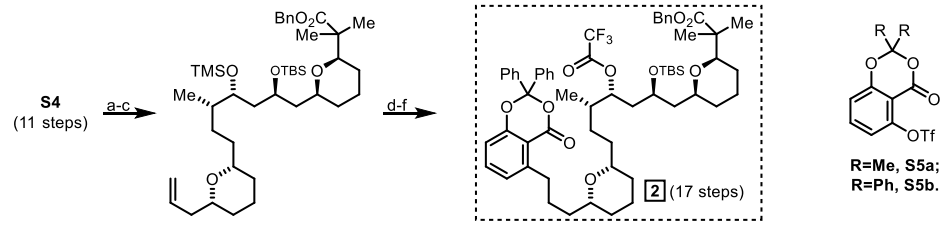
B. De Brabander *et al. Org. Lett.* **2002**, *4*, 481.; *Org. Lett.* **2005**, *7*, 2791.

Fragment 1



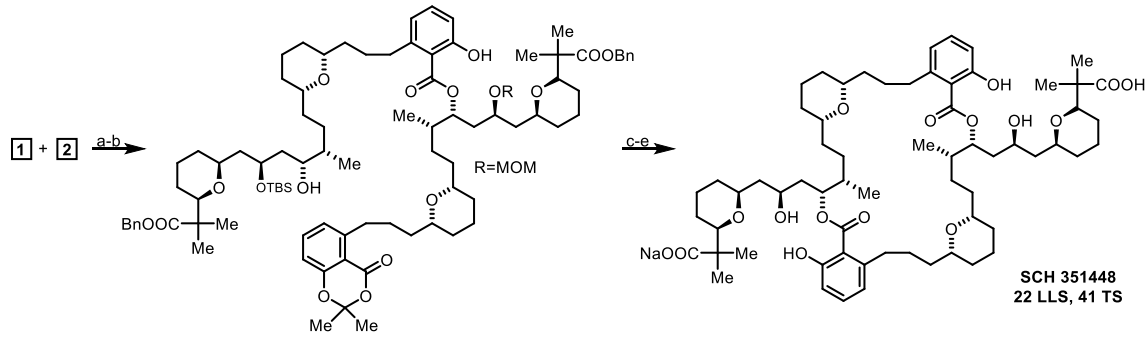
Key: (a) (+)-Ipc$_2$BOMe, allylMgBr, -78 °C, Et_2O; (b) CH_2=CHCOCl, *i*-Pr_2NEt, DMAP,CH_2Cl_2; (c) 5 mol % Grubbs' 2nd generation catalyst, CH_2Cl_2, 4 h, rt; (d) $NiCl_2$-6H_2O, $NaBH_4$, THF, 0 °C, 2 h; (e) DIBAL-H, CH_2Cl_2, -78 °C, 1 h; (f) 1-triphenylphosphoranylidene-2-propanone, MeCN, 90 °C, 24 h; (g) *t*-BuOK, THF, 0 °C, 5-10 min; (h) *B*-allyl bis(4-isocaranyl)borane, Et_2O, -78 °C; (i) *t*-BuOK, THF, -35 °C; (j) $LiAlH_4$, Et_2O, 0 °C; (k) PCC, CH_2Cl_2, 3 h, RT; (l) (2*S*)-*N*-propionyl bornanesultam, $TiCl_4$, *i*-Pr_2NEt, -78 °C; then add **S2**, -78 °C; (m) PhOC(S)Cl, py, CH_2Cl_2, 14 h, RT; (n) Bu_3SnH, 10% AIBN, PhH, 7 h, reflux; (o) DIBAL-H, CH_2Cl_2, -78 °C, 1 h; then MeOH, -78 °C, 10 min; or $LiAlH_4$, Et_2O; then Dess-Martin periodinane, CH_2Cl_2; (p) Et_2BOTf, Et_2O, -78 °C; then **S3** -78 °C; (q) MeCHO, SmI_2, THF, -10 °C; (r) MOMCl, ^{i}Pr_2NEt, DCM; (s) K_2CO_3, MeOH; (t) TMSCl, NEt_3, DCM; (u) 9-BBN, THF; **S5a**, $PdCl_2$dppf, aq. K_3PO_4, DMF/THF; (v) HF-py, THF.

Fragment 2



Key: (a) $Me_4N(AcO)_3BH$, HOAc, MeCN, -10 °C; (b) TBSCl, imid., DMF; (c) TMSCl, NEt_3, DCM; (d) 9-BBN, THF; **S5b**, $PdCl_2$dppf, aq. K_3PO_4, DMF/THF; (e) HF-py, THF; (f) TFAA, py, DCM.

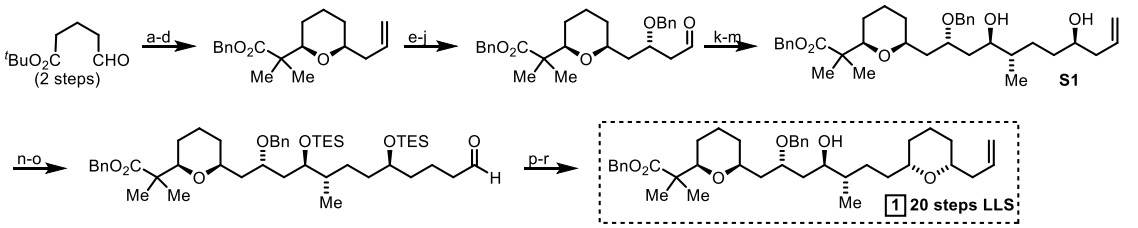
Fragment Union and End Game



Key: (a) hν (300 nm), DCM, 0.1 M, 1 h, rt; (b) NH_3, MeOH; (c) NaHMDS, THF, -78 °C; (d) 10% Pd/C, H_2, MeOH; (e) 48% aq. HF, MeCN, rt, 48 h; hexane extraction from aq. HCl (4 N, sat. with NaCl).

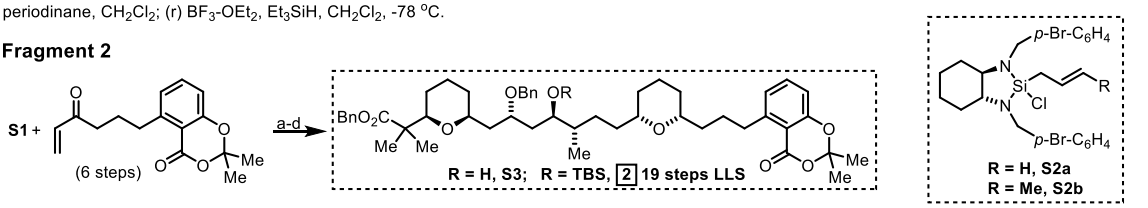
C. Leighton *et al. Org. Lett.* **2005**, *7*, 3809.

Fragment 1



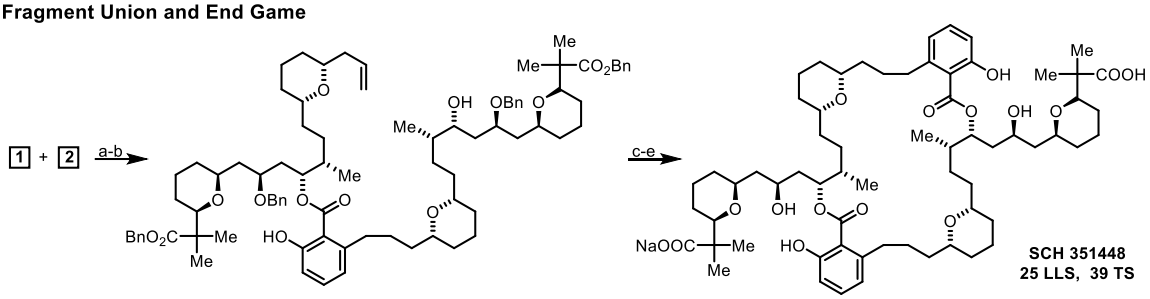
Key: (a) *ent*-**S2a**, -10 °C, CH_2Cl_2; (b) *p*-TsOH, PhH, reflux; (c) $BnO_2CCH(CH_3)_2$, LDA, THF, 0 °C; (d) BF_3-OEt_2, Et_3SiH, CH_2Cl_2, -78 °C; (e) OsO_4, NMO, Acetone, H_2O; (f) $NaIO_4$, THF, H_2O; (g) (+)-*B*-methoxyldiisopinocamphenylborane, AllylMgBr, Et_2O, -100 °C; (h) NaH, BnBr, DMF, 0 °C; (i) OsO_4, NMO, Acetone, H_2O; (j) $NaIO_4$, THF, H_2O; (k) **S2b**, CH_2Cl_2, 0 °C; (l) $(Allyl)_2Si(NEt_2)H$, CH_2Cl_2; (m) $Rh(acac)(CO)_2$, 900 psi CO, PhH, 65 °C, *n*-Bu_4NF, THF, reflux; (n) TESCl, Et_3N, CH_2Cl_2, -78 °C; (o) $Rh(acac)(CO)_2$, NIXANTPHOS, 600 psi H_2/CO, THF, 60 °C; (p) AllylBr, Zn, aq. NH_4Cl, THF; (q) Dess-Martin periodinane, CH_2Cl_2; (r) BF_3-OEt_2, Et_3SiH, CH_2Cl_2, -78 °C.

Fragment 2



Key: (a) Grubbs' II Cat., CH_2Cl_2, reflux; (b) Lindlar Cat., H_2, MeOH; (c) BF_3-OEt_2, Et_3SiH, CH_2Cl_2, -78 °C; (d) TBSOTf, Et_3N, CH_2Cl_2.

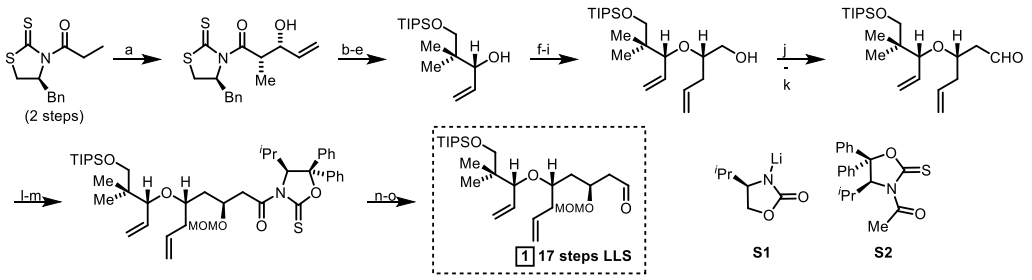
Fragment Union and End Game



Key: (a) **2**, NaHMDS, THF, 0 °C; then **3**; (b) HCl, Et_2O, MeOH; (c) **S3**, NaHMDS, THF, 0 °C; (d) Grubbs' II Cat., CH_2Cl_2, reflux; (e) Pd/C, H_2, MeOH, EtOAc.

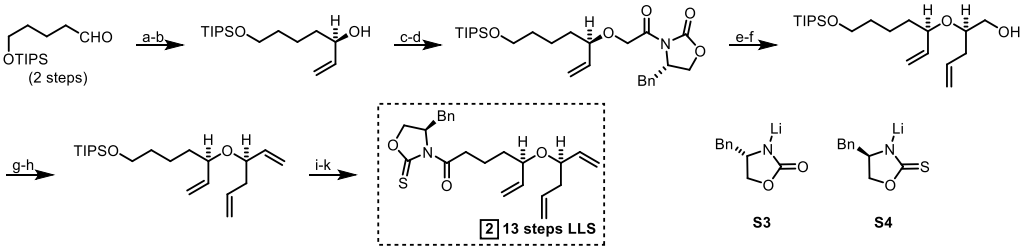
D. Crimmins *et al. Org. Lett.* **2006**, *8*, 2887.

Fragment 1



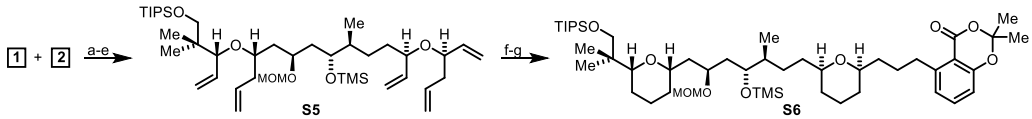
Key: (a) $TiCl_4$, (-)sparteine, NMP, acrolein, CH_2Cl_2, -78 °C; (b) ^{t}BuOH, imidazole; (c) LDA, MeI, THF, -30 °C; (d) $LiAlH_4$, Et_2O, (e) TIPSCl, imidazole; (f) $BrCH_2Co_2H$, NaH; (g) **S1**, PivCl, THF; (h) $NaN(SiMe_3)_2$, THF, allyl iodide, -40 °C; (i) $LiBH_4$, MeOH, Et_2O; (j) $Me_2CCN(OH)$, DEAD, Ph_3P, THF; (k) $^i Bu_2AlH$, CH_2Cl_2; (l) **S2**, $TiCl_4$, (-)-sparteine, NMP, CH_2Cl_2, -78 °C; (m) MOMCl, CH_2Cl_2, $^i Pr_2NEt$, 0 °C; (n) $LiBH_4$, MeOH, Et_2O; (o) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N.

Fragment 2

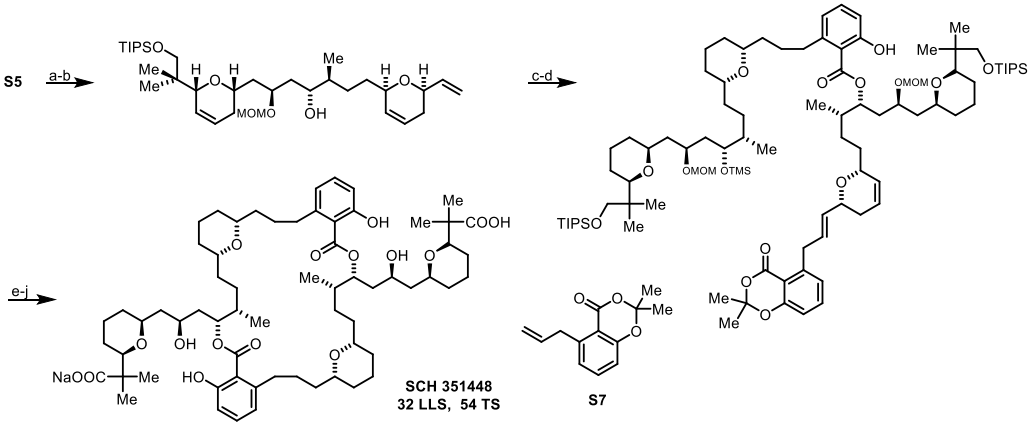


Key: (a) CH_2=$CHMgBr$, THF; (b) $Ti(O^iPr)_4$, (+)-DCHT, ^{t}BuOOH, CH_2Cl_2; (c) $BrCH_2CO_2H$, NaH, THF; (d) **S3**, PivCl, THF; (e) $NaN(SiMe_3)_2$, THF, allyl iodide, -40 °C; (f) $LiBH_4$, MeOH, Et_2O; (g) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N; (h) Ph_3PCH_3Br, ^{t}BuOK, $PhCH_3$; (i) $^n Bu_4NF$, THF, (j) H_2CrO_4, acetone; (k) **S4**, $(COCl)_2$, DMF, CH_2Cl_2.

Fragment Union and End Game



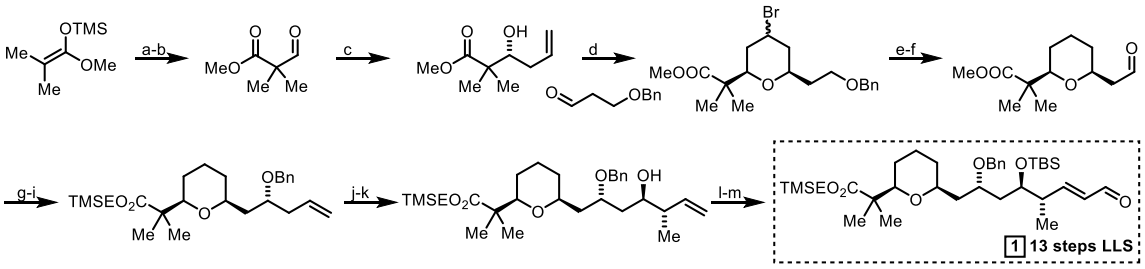
Key: (a) **1**, $TiCl_4$, (-)-sparteine, NMP, CH_2Cl_2, -78 °C; (b) TMSCl, Et_3N, DMAP, CH_2Cl_2; (c) $NaBH_4$, THF, H_2O; (d) MsCl, Et_3N, CH_2Cl_2; (e) $LiEt_3BH$, THF; (f) **S7**, $Cl_2(PCy_3)(IMes)Ru$=$CHPh$, CH_2Cl_2, 40 °C; (g) Rh/Al_2O_3, H_2.



Key: (a) PPTS, MeOH, 0 °C; (b) $Cl_2(PCy_3)(IMes)Ru$=$CHPh$, CH_2Cl_2, 40 °C; (c) **S6**, $NaN(SiMe_3)_2$, THF; (d) **S7**, $Cl_2(PCy_3)(IMes)Ru$=$CHPh$, CH_2Cl_2, 40 °C; (e) Rh/Al_2O_3, H_2; (f) PPTS, MeOH; (g) NaHMDS; (h) $^n Bu_4NF$, THF; (i) TPAP, NMO; $NaClO_2$; (j) HF, CH_3CN, 4N HCl, NaCl.

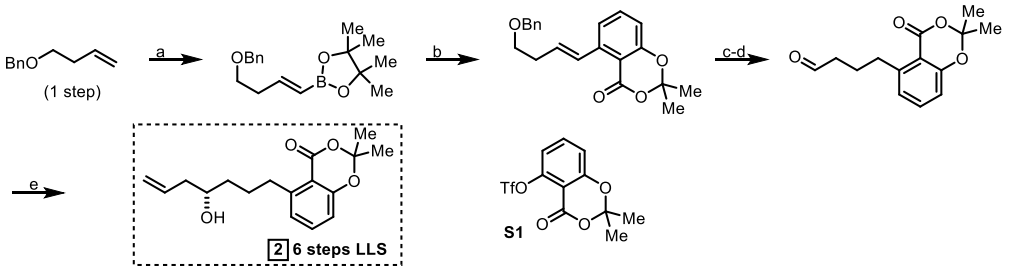
E. Loh *et al. Chem. Commun.* **2007**, 939.

Fragment 1



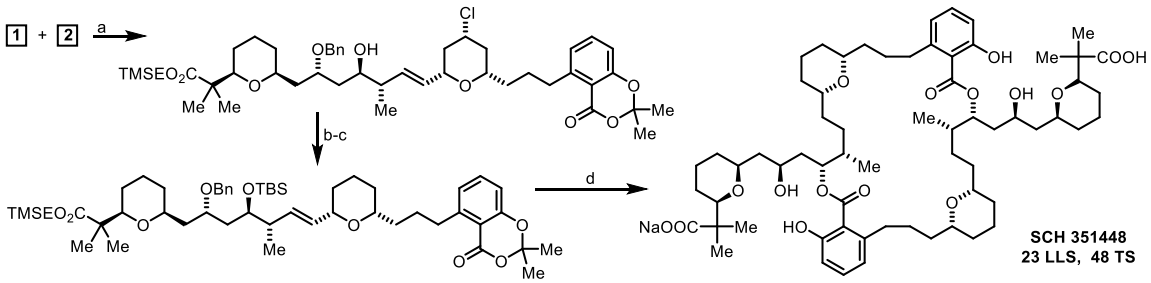
Key: (a) HCOH, $InCl_3$, 24 h; (b) PCC, CH_2Cl_2, 0 °C, 12 h; (c) (+)-DIPBr, AllylMgBr, -78 °C; (d) $InBr_3$, TMSBr, -78 °C; (e) Pd/C, $NaHCO_3$, H_2, 24 h; (f) DMP, CH_2Cl_2, 0 °C, 0.5 h; (g) (+)-DIPBr, AllylMgBr, THF, -78 °C; (h) BnBr, NaH, DMF, 0 °C, 0.5 h; (i) $Ti(O^iPr)_4$, TMSEOH, reflux, 48 h; (j) OsO_4, NMO, 12 h, then $NaIO_4$, 0.5 h; (k) ^{n}BuLi, (*E*)-But-2-ene, KO^{t}Bu, B(^{d}Ipc)$_2$OMe, BF_3-OEt_2, -78 °C; (l) Acrolein, Hoveyda-Grubbs' II Cat., CH_2Cl_2, reflux, 12 h; (m) TBSOTf, 2,6-Lutidine, Et_3N, 0 °C, 0.5 h.

Fragment 2



Key: (a) Grubbs' II Cat., CH_2Cl_2, reflux, 8 h; (b) **S1**, Pd(dppf)Cl_2, K_3PO_4, THF, reflux, 12 h; (c) Pd/C, H_2, 4 h; (d) DMP, 0 °C, 0.5 h; (e) (+)-DIPBr, AllylMgBr, -78 °C.

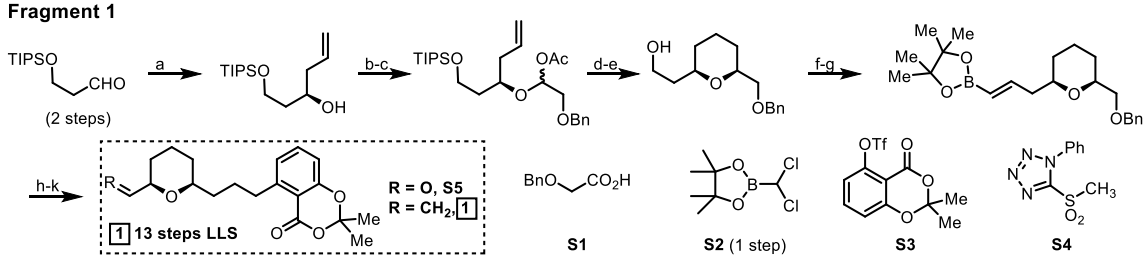
Fragment Union and End Game



Key: (a) In(OTf)$_3$, TMSCl, CH_2Cl_2, -78 °C to -40 °C, 4 h; (b) ACCN, Bu_3SnH, PhMe, reflux, 12 h; (c) TBSOTf, 2,6-Lutidine, Et_3N, 0 °C, 0.5 h; (d) Lee *et al. J. Am. Chem. Soc.* **2004**, *126*, 2680.; *J. Org. Chem.* **2005**, *70*, 6321.

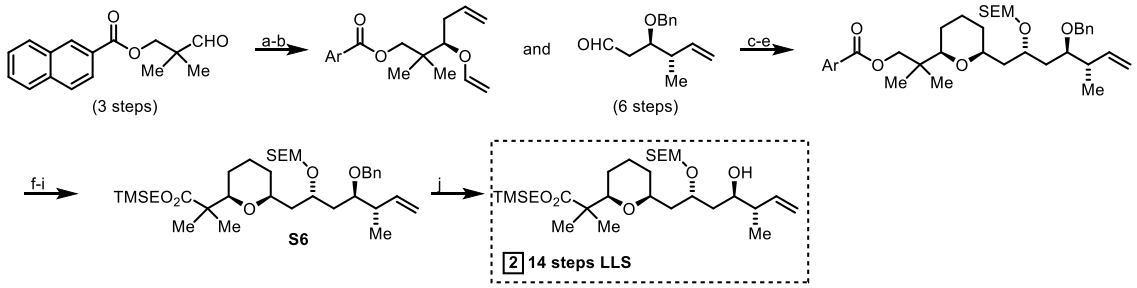
F. Rychnovsky *et al. Org. Lett.* **2008**, *10*, 3101.

Fragment 1



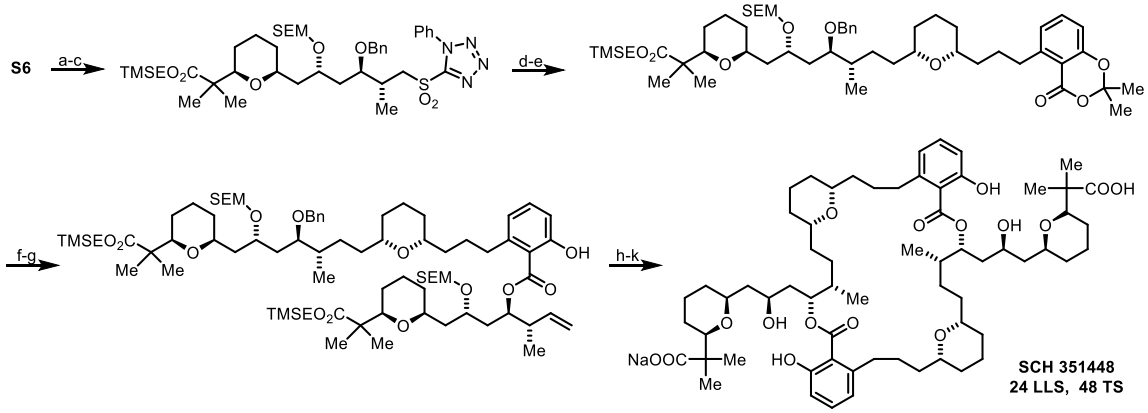
Key: (a) $AllylSnBu_3$, $Ti(O^iPr)_4$, (*R*)-BINOL; (b) **S1**,DCC, DMAP; (c) DIBAL-H; Ac_2O, DMAP; (d) $SnBr_4$, -78 °C; (e) Bu_3SnH, $NaBH_4$, EtOH; then 3 N HCl; (f) DMP, CH_2Cl_2; (g) $CrCl_2$, LiI, **S2**, THF; (h) **S3**, $PdCl_2(dppf)$, K_3PO_4, THF; (i) Pd/C, H_2, MeOH; (j) DMP, CH_2Cl_2; (k) **S4**, NaHMDS.

Fragment 2



Key: (a) AllylTMS, TiF_4, (*R*)-BINOL; (b) Ethyl vinyl ether, $Hg(TFA)_2$; (c) $TiBr_4$, 2,6-DTBMP, CH_2Cl_2, -78 °C; (d) Bu_3SnH, AIBN; (e) SEMCl, DIPEA; (f) NaOH, MeOH; (g) TPAP, NMO; (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; (i) $TMSCH_2CH_2OH$, DIAD, PPh_3; (j) DDQ, pH 7 buffer, CH_2Cl_2.

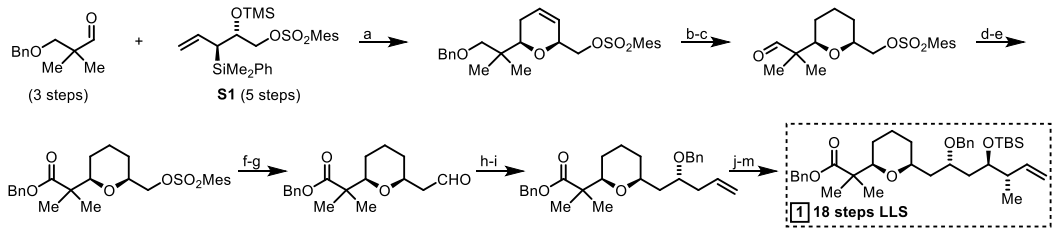
Fragment Union and End Game



Key: (a) O_3, CH_2Cl_2, -78 °C; PPh_3; $NaBH_4$; (b) PPh_3, DIAD, 1-phenyl-1*H*-tetrazole-5-thiol; (c) 30% H_2O_2, EtOH, $(NH_4)_6Mo_7O_{24}$-$4H_2O$; (d) **S5**, NaHMDS, THF; (e) *p*-$TsNHNH_2$, NaOAc, 100 °C; (f) **2**, NaHMDS; (g) DDQ, pH 7 buffer; (h) **1**, NaHMDS, THF; (i) Grubbs-Hoveyda Cat., CH_2Cl_2, reflux; (j) *p*-$TsNHNH_2$, NaOAc, 100 °C; (k) TFA, CH_2Cl_2; 4 N HCl, NaCl, hexanes.

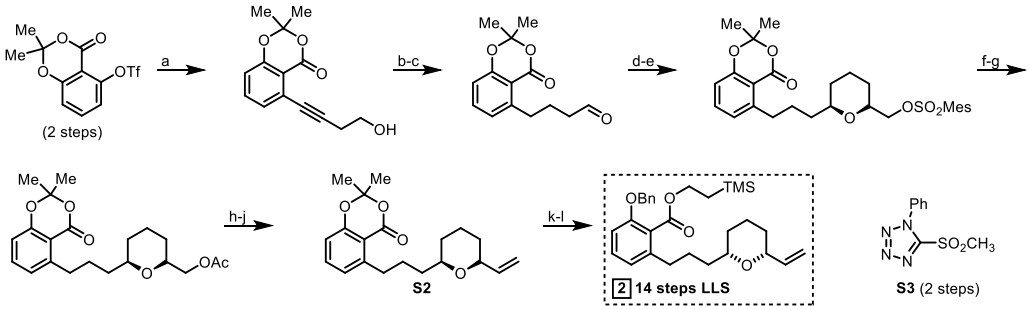
G. Panek *et al. Org. Lett.* **2011**, *13*, 4652.

Fragment 1



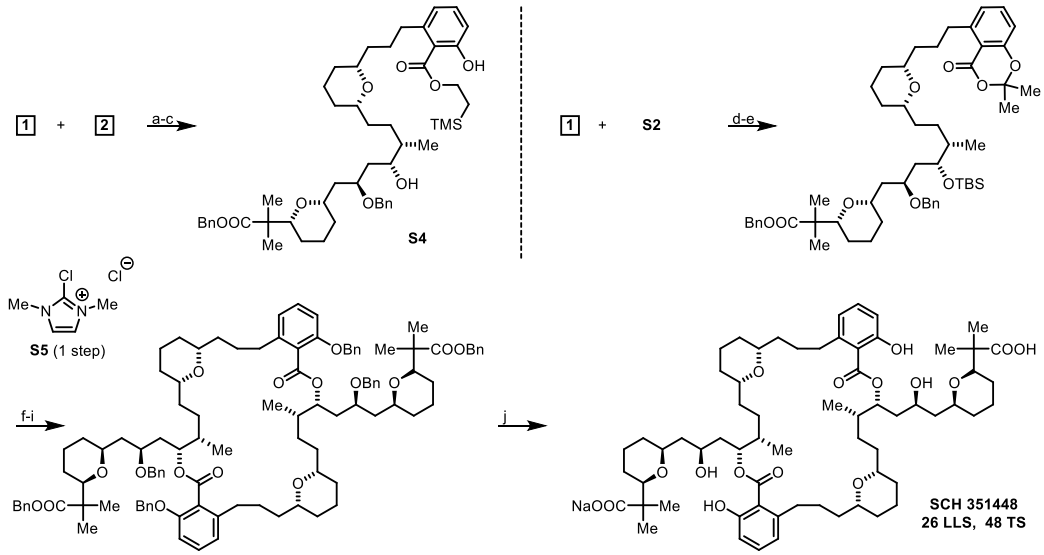
Key: (a) TMSOTf, CH_2Cl_2/PhH (3:1), -78 °C; (b) 10% Pd/C, H_2; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (d) $NaClO_2$-NaH_2PO_4-H_2O, 2-methyl-2-butene, ^{t}BuOH; (e) BnBr, DBU, MeCN; (f) NaCN, DMF, 60 °C; (g) Raney-Ni, NaH_2PO_2, Pyr/HOAc/H_2O (2:1:1), 50 °C; (h) $Ipc_2BAllyl$, THF, -78 °C; (i) BnBr, NaH, DMF, 0 °C; (j) OsO_4, NMO, acetone/H_2O (3:1); (k) $NaIO_4$, THF; (l) ^{t}BuOK, *trans*-2-butene, ^{n}BuLi, $B(^d Ipc)_2OMe$, THF, -78 °C; (m) TBSOTf, lutidine.

Fragment 2



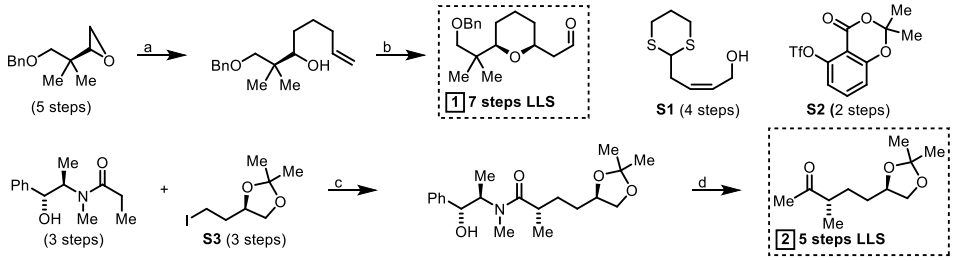
Key: (a) 3-Butyn-1-ol, DIPA, $Pd(PPh_3)_2Cl_2$, CuI, dioxane, 85 °C; (b) 10% Pd/C, H_2, MeOH; (c) PCC, CH_2Cl_2; (d) **S1**, TMSOTf, CH_2Cl_2/PhH (3:1), -78 °C; (e) 10% Pd/C, H_2, MeOH; (f) NaI, acetone, reflux; (g) AgOAc, DMF, 100 °C; (h) $Sc(OTf)_3$, MeOH/H_2O (4:1); (i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C; (j) **S3**, NaHMDS, THF, -78 °C; (k) 2-(Trimethylsilyl)ethanol, NaHMDS, THF; (l) BnBr, Cs_2CO_3.

Fragment Union and End Game



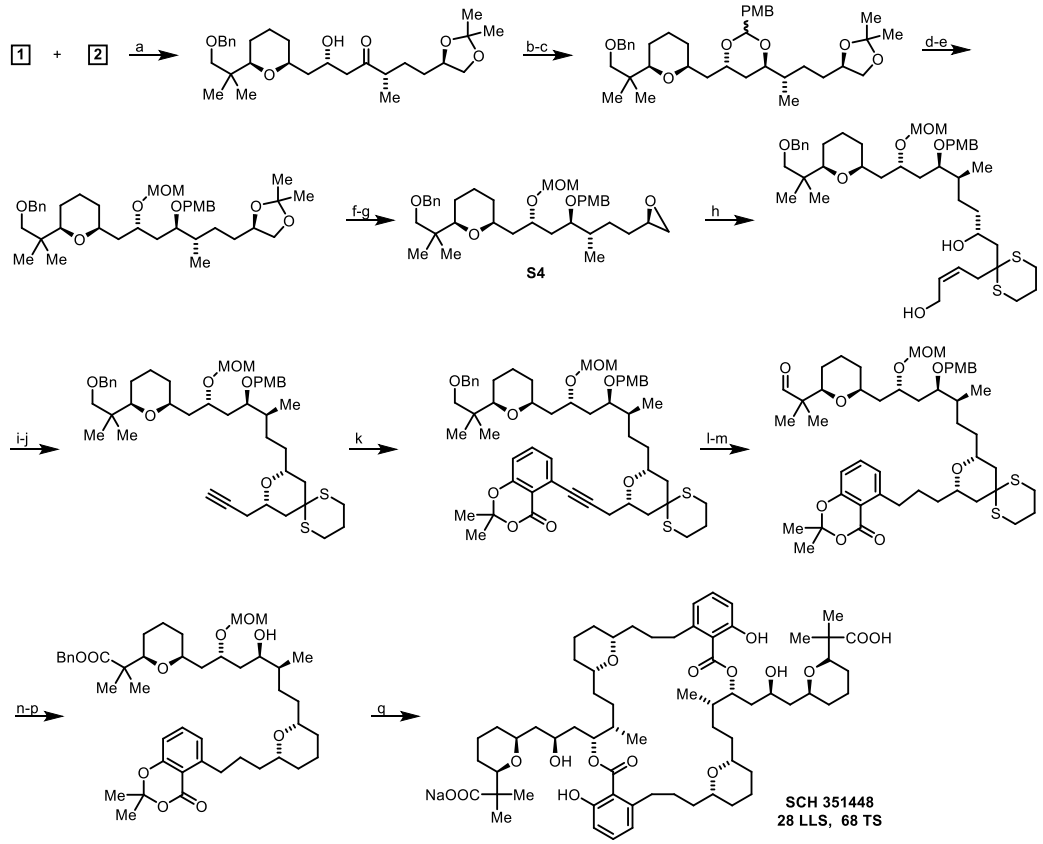
Key: (a) Grubbs-Hoveyda II, C_6H_5Cl, 85 °C; (b) *p*-$TsNHNH_2$, NaOAc, DME/H_2O, reflux; (c) HCl, MeOH; (d) Grubbs-Hoveyda II, C_6H_5Cl, 70 °C, 12 h; (e) *p*-$TsNHNH_2$, NaOAc, DME/H_2O (1:1), 100 °C; (f) **S4**, NaHMDS, THF, -78 °C; (g) BnBr, Cs_2CO_3, DMF; (h) TBAF, THF, 0 °C; (i) DMAP, CH_2Cl_2, 42 °C, **S5**; (j) Pd/C, H_2, MeOH, then 4 N HCl in NaCl.

Fragment 1 and 2



Key: (a) 3-Butenylmagnesium bromide, CuI, THF, -20 °C, 1 h; (b) crotonaldehyde, Hoveyda-Grubbs' II, toluene, 110 °C, 18 h; (c) LDA, LiCl, THF, -78 °C, 1 h, then **S3**, 25 °C, 3 h; (d) CH_3Li, THF, 0 °C, 0.5 h.

Fragment Union and End Game



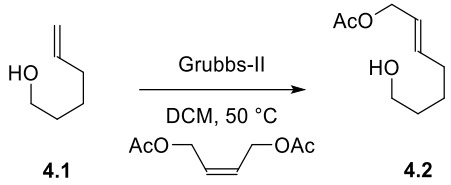
Key: (a) (-)-Ipc_2BCl, Et_3N, Et_2O, 0 °C, 1 h, then **1**, -78 °C, 2 h, -20 °C, 16 h; (b) $Me_4NBH(OAc)_3$, CH_3CN/HOAc, 25 °C, 4 h; (c) *p*-anisaldehyde dimethyl acetal, PPTS, CH_2Cl_2, 25 °C, 2 h; (d) DIBAL, toluene, -20 °C, 1 h; (e) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 25 °C, 24 h; (f) PPTS, $CHCl_3$/MeOH, 25 °C, 48 h; (g) NaH, 1-tosylimidazole, THF, 25 °C, 6 h; (h) **S1**, ^{t}BuLi, THF/HMPA (4:1), -78 °C, 5 min; then **S4**, -78 °C, 1 h; (i) MnO_2, CH_2Cl_2, 25 °C, 8 h; (j) *p*-TsN_3, K_2CO_3, $(MeO)_2P(O)CH_2COCH_3$, CH_3CN, MeOH, 25 °C, 18 h; (k) **S2**, NaHMDS, B-OMe-9-BBN, KBr, $PdCl_2$(dppf), THF, reflux, 3 h; (l) H_2, Raney-Ni, EtOH, 50 °C, 40 h; (m) Dess-Martin periodinane, pyridine, CH_2Cl_2, 25 °C, 5 h; (n) $NaClO_2$, NaH_2PO_4-H_2O, 2-methyl-2-butene, ^{t}BuOH/H_2O (1/1), 25 °C, 4 h; (o) BnBr, Cs_2CO_3, CH_3CN, 25 °C, 2 h; (p) DDQ, CH_2Cl_2/H_2O, 25 °C, 1 h; (q) De Brabander *et al. Org. Lett.* **2002**, *4*, 481.; *Org. Lett.* **2005**, *7*, 2791.

General Information

All reactions were carried out in oven- or flame-dried flasks, under an inert atmosphere of argon or nitrogen if anhydrous conditions were required. Anhydrous solvents were transferred by oven-dried syringes and needles. Reagents obtained from Acros, Sigma-Aldrich, Alfa Aesar, Fisher Scientific, Takasago, Oakwood, or Strem Fine Chemicals suppliers were used directly as supplied or following purification according to procedures described by Amarego and Chai.[29] Tetrahydrofuran, dichloromethane, diethyl ether, and toluene were distilled prior to use. Thin layer chromatography (TLC) was performed on Dynamic Adsorbents F254 0.25 mm precoated silica gel plates. Compounds were visualised under UV light and by staining with potassium permanganate, or *para*-anisaldehyde solution. Flash column chromatography was performed using silica gel (40–63 μm, Silicycle) and using head pressure by means of a positive pressure from an air line, according to Still.[30] Infra-red spectra were recorded on a Thermo Nicolet 380 spectrometer. High-resolution mass spectra were recorded on an Agilent Technologies 6530 Accurate Mass Q-Tof LC/MS instrument for electrospray ionisation (ESI) or a Micromass Autospec Ultima instrument for chemical ionization (CI) and are reported as a ratio of mass to charge (m/z) in Daltons. Specific optical rotations were recorded on an Atago AP-300 automatic polarimeter at the sodium line (589.3 nm) in $CHCl_3$. Solution concentrations are given in the units of 10^{-2} g mL^{-1}. ^1H NMR spectra were recorded on an Agilent MR (400 MHz), Varian DirectDrive (400 MHz) spectrometer in $CDCl_3$ or CD_2Cl_2 at ambient temperature. Chemical shifts are quoted to two decimal places in parts per million (ppm) with splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m). Coupling constants, *J*, are quoted to one decimal place in Hz. ^{13}C NMR spectra were recorded on an Agilent MR (100 MHz), Varian DirectDrive (100 MHz spectrometer in $CDCl_3$ or CD_2Cl_2 with broadband decoupling. Chemical shifts are quoted to one decimal place in parts per million (ppm). All NMR chemical shifts were referenced to residual solvent peaks ($CDCl_3$, δ_H 7.26 ppm, δ_C 77.0 ppm; CD_2Cl_2 δ_H 5.32 ppm, δ_C 53.8 ppm).

Experimental Procedure and Characterization of Intermediates:

(*E*)-7-hydroxyhept-2-en-1-yl acetate (4.2)



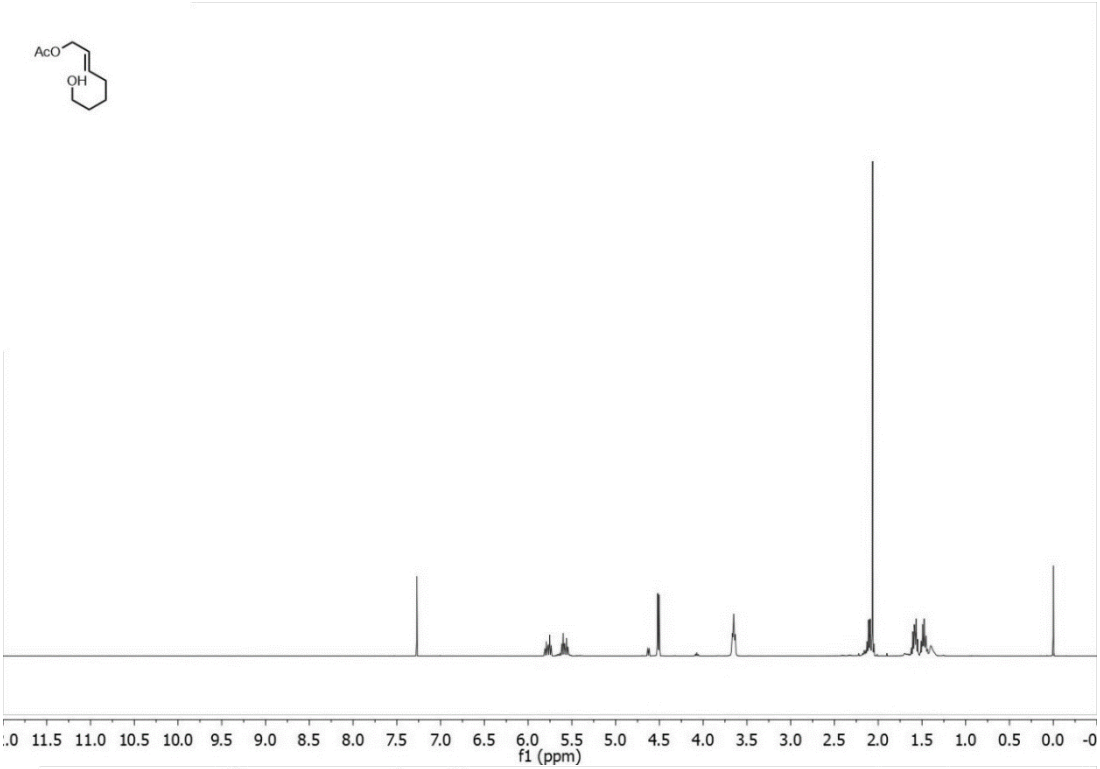
To a sealed tube under an argon atmosphere charged with hex-5-en-1-ol (**4.1**) (400.6 mg, 4.00 mmol, 100 mol%) and *cis*-1,4-diacetoxy-2-butene (688.7 mg, 16.00 mmol, 400 mol%) was added freshly distilled CH_2Cl_2 (22 mL, 0.18 M). The Grubbs' second generation catalyst [$Cl_2(PCy_3)(IMes)Ru{=}CHPh$] (101.9 mg, 0.12 mmol, 3 mol%) was added in one portion. The septum was quickly replaced with a screw cap, and the reaction mixture was allowed to stir in an oil bath at 50 ºC for 20 h. The reaction mixture was allowed to cool ambient temperature, was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 4:1 to 2:1) to furnish the title product **4.2** in 87% yield (600 mg, 3.48 mmol, *E:Z*=7:1). Spectral data is reported for the major isomer.

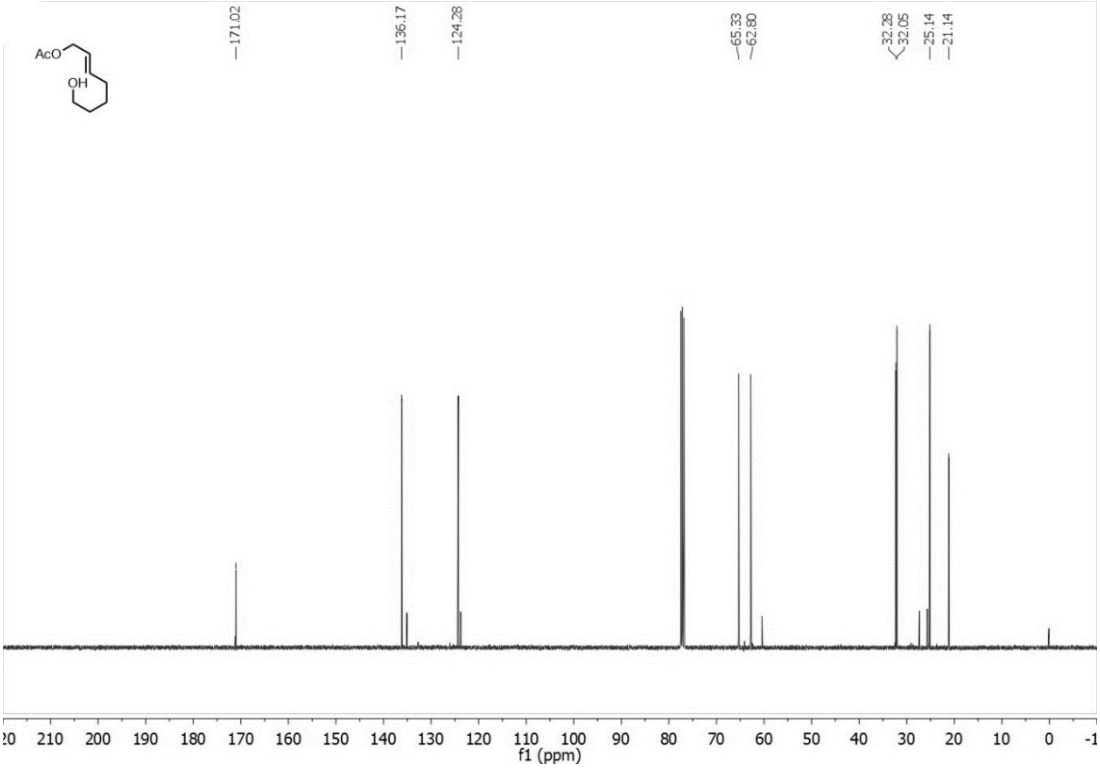
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82–5.71 (m, 1H), 5.58 (dtt, *J* = 15.6, 6.5, 1.4 Hz, 1H), 4.51 (dd, *J* = 6.5, 1.1 Hz, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.14–2.07 (m, 2H), 2.06 (s, 3H), 1.64–1.53 (m, 2H), 1.52–1.44 (m, 2H), 1.40 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 136.2, 124.3, 65.3, 62.8, 32.3, 32.1, 25.1, 21.1.

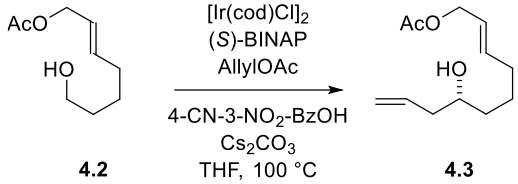
HRMS (ESI) Calcd. for $C_9H_{16}O_3Na$ $[M+Na]^+$: 195.0992, Found: 195.0996.

FTIR (neat): 3381, 2934, 1736, 1364, 1227, 1023, 969 cm^{-1}.


AcO
OH
f1 (ppm)


AcO
OH
171.02
136.17
124.28
65.33
62.80
32.28
32.05
25.14
21.14
f1 (ppm)

(*R*,*E*)-7-hydroxydeca-2, 9-dien-1-yl acetate (4.3)



4.2 **4.3**

To a sealed tube under an argon atmosphere charged with alcohol **4.2** (390.0 mg, 2.27 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (38.3 mg, 0.057mmol, 2.5 mol%), (*S*)-BINAP (71.0 mg, 0.114 mmol, 5.0 mol%), Cs_2CO_3 (148.0 mg, 0.45 mmol, 20 mol%) and 4-CN-3-NO_2-BzOH (39.3 mg, 0.23 mmol, 10 mol%) was added freshly distilled THF (11.4 mL, 0.2 M) and allyl acetate (454.5 mg, 4.54 mmol, 200 mol%). The septum was quickly replaced with a screw cap and the reaction mixture was allowed to stir in an oil bath at 100 °C for 72 h. The reaction mixture was allowed to cool to ambient temperature, and was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 8:1 to 4:1) to furnish the title product **4.3** in 62% yield (298.8 mg, 1.41 mmol, 96% *ee*), catalyst was recovered using DCM/ether, 4:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.73 (m, 2H), 5.58 (dtt, *J* = 15.4, 6.6, 1.4 Hz, 1H), 5.23–5.09 (m, 2H), 4.51 (dt, *J* = 6.5, 1.0 Hz, 2H), 3.72–3.61 (m, 1H), 2.31 (dddt, *J* = 13.7, 6.2, 4.2, 1.3 Hz, 1H), 2.19–2.07 (m, 3H), 2.06 (s, 3H), 1.71 (br s, 1H), 1.63–1.53 (m, 1H), 1.53–1.43 (m, 3H).

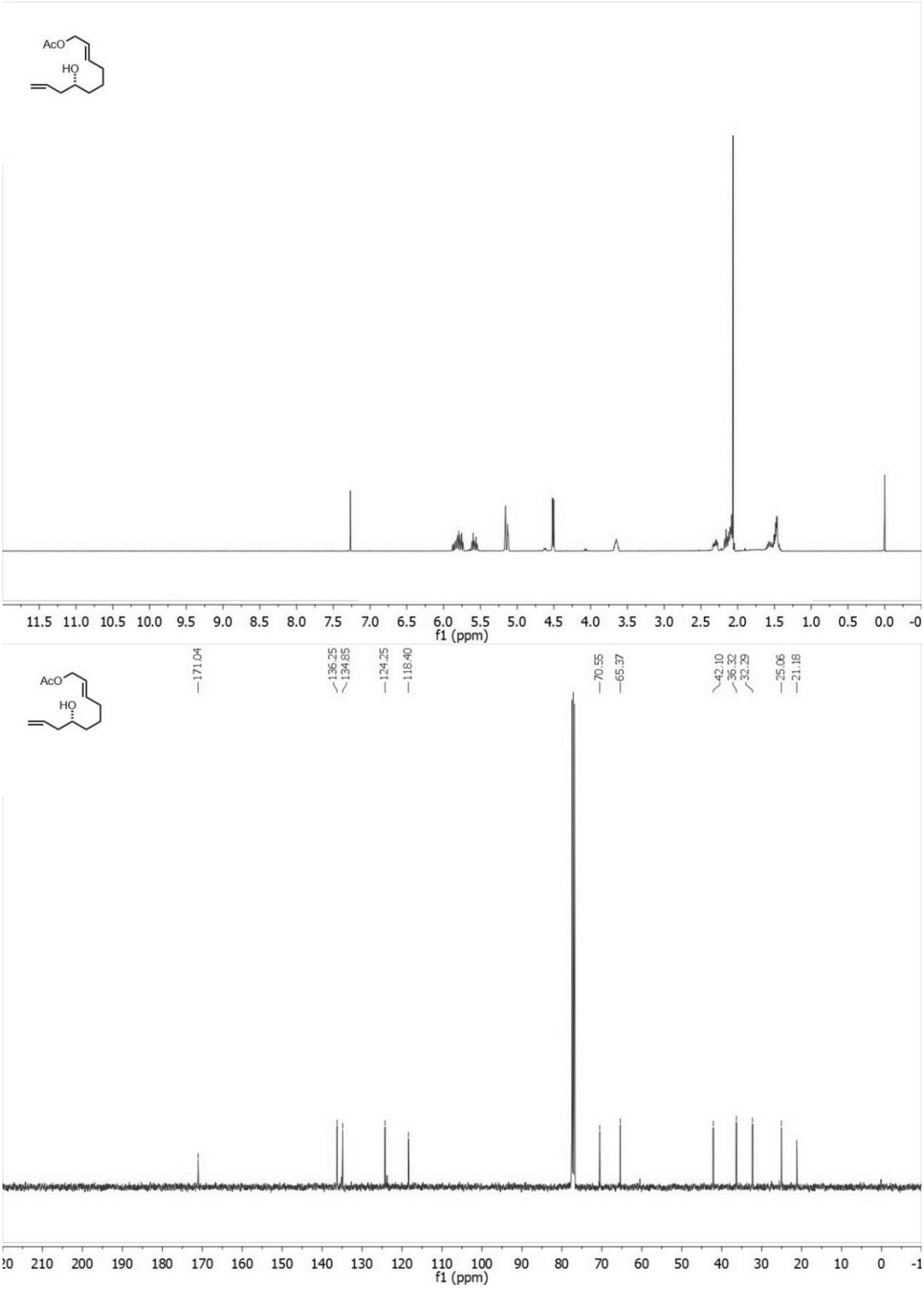
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 136.3, 134.9, 124.3, 118.4, 70.6, 65.4, 42.1, 36.3, 32.3, 25.1, 21.2.

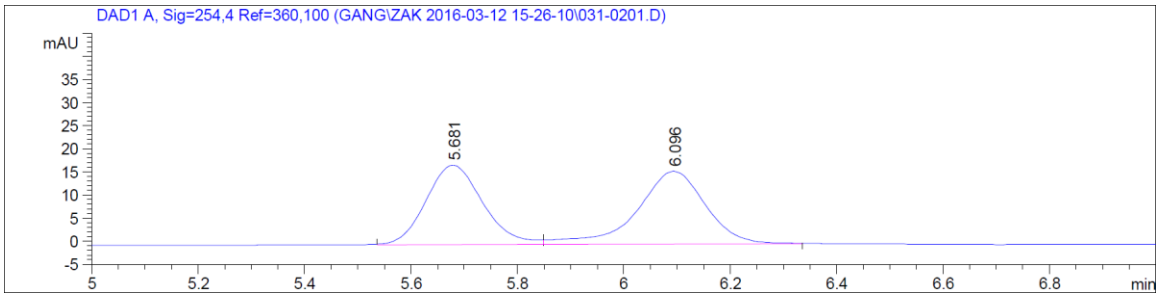
HRMS (ESI) Calcd. for $C_{12}H_{20}O_3Na$ $[M+Na]^+$: 235.1305, Found: 235.1309.

FTIR (neat): 3420, 2933, 1738, 1437, 1363, 1231, 1024, 969, 913 cm^{-1}.

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 87:13, 1.00 mL/min, 254 nm), *ee* =96% (Alcohol **3** was protected with benzyl group).

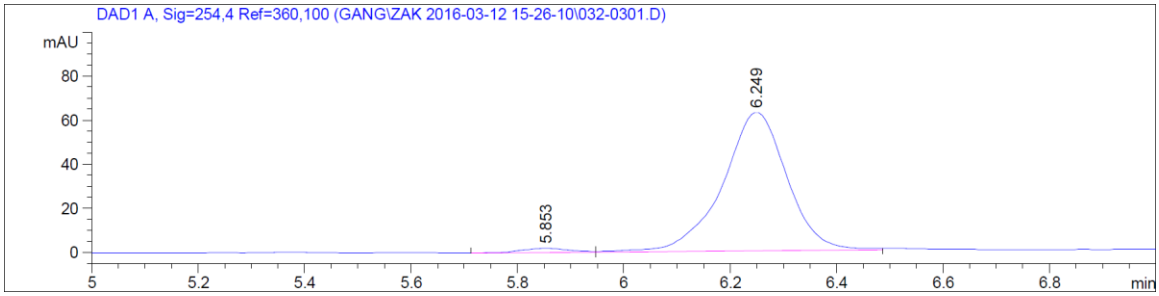
$[\alpha]^{20}_D$ = +10.00 ° (c 1.0, $CHCl_3$).


AcO
HO
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)
AcO
HO
171.04
136.25
134.85
124.25
118.40
70.55
65.37
42.10
36.32
32.29
25.06
21.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

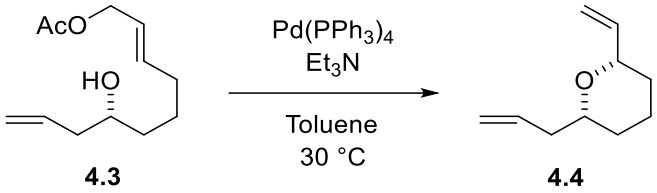
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.681	BV	0.1143	126.99027	17.17166	47.3036
2	6.096	VB	0.1347	141.46756	15.76023	52.6964
Totals :				268.45783	32.93188	



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.853	BV	0.0964	11.10787	1.83955	2.0613
2	6.249	VB	0.1258	527.78131	62.97322	97.9387
Totals :				538.88918	64.81277	

(2*R*,6*S*)-2-allyl-6-vinyltetrahydro-2*H*-pyran (4.4)



4.3 **4.4**

To a sealed tube under an argon atmosphere charged with $Pd(PPh_3)_4$ (208.0 mg, 0.18 mmol, 18 mol%) and toluene (8.30 mL) was added Et_3N (202.4 mg, 2.0 mmol, 200 mol%). Alcohol **4.3** in toluene (4.2 mL) was added to the reaction mixture. The reaction mixture was allowed to stir for at 30 °C for 48 h. The reaction mixture was directly subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 100:0 to 25:1) to furnish the title product **4.4** in 65% yield (98.9 mg, 0.65 mmol, 6:1 *dr*).

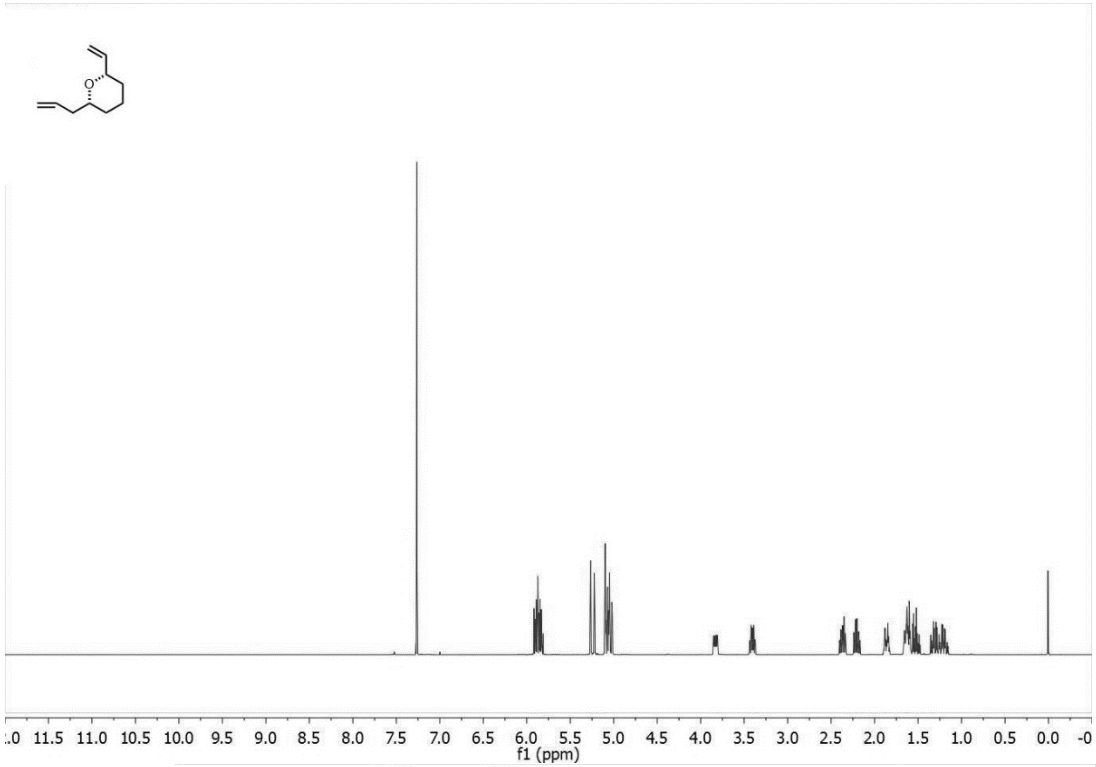
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94–5.79 (m, 2H), 5.24 (dt, *J* = 17.3, 1.7 Hz, 1H), 5.13–4.99 (m, 3H), 3.83 (dddd, *J* = 10.7, 5.3, 2.6, 1.5 Hz, 1H), 3.40 (dtd, *J* = 11.2, 6.3, 2.0 Hz, 1H), 2.37 (dtt, *J* = 14.3, 6.5, 1.5 Hz, 1H), 2.20 (dddt, *J* = 14.0, 7.6, 6.4, 1.2 Hz, 1H), 1.92–1.80 (m, 1H), 1.70–1.57 (m, 2H), 1.52 (tt, *J* = 13.0, 3.9 Hz, 1H), 1.37–1.14 (m, 2H).

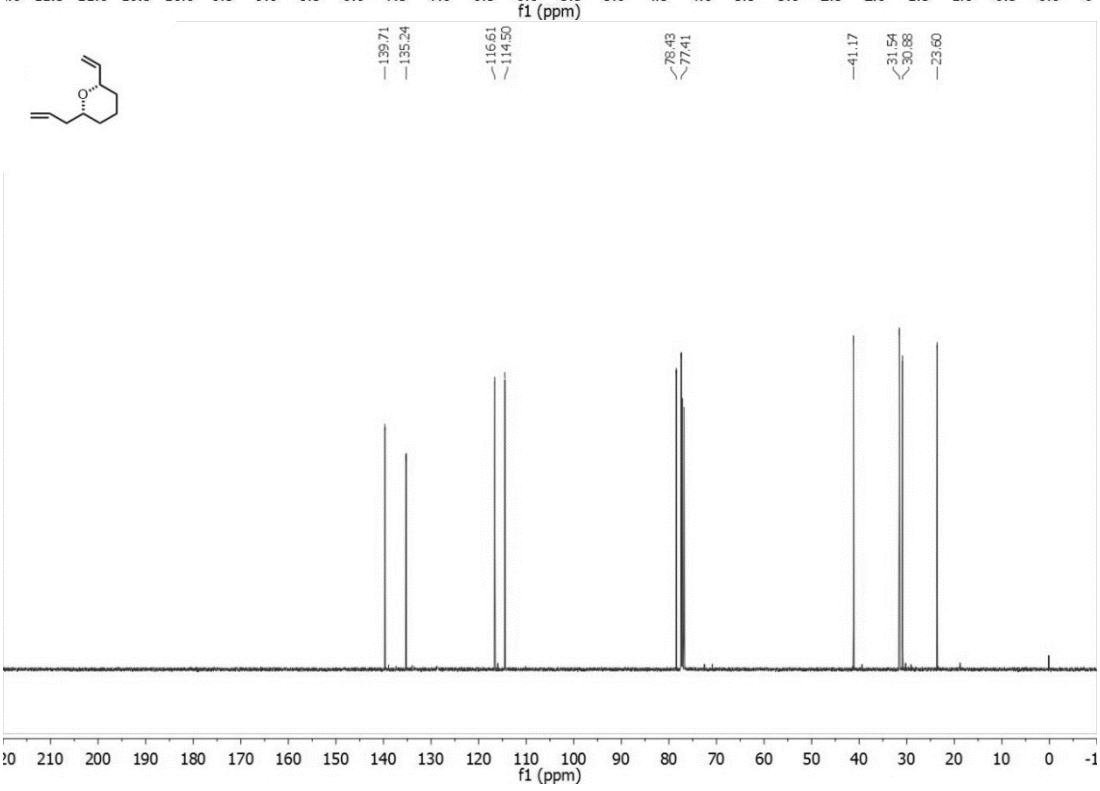
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 135.2, 116.6, 114.5, 78.4, 77.4, 41.2, 31.5, 30.9, 23.6.

HRMS (CI) Calcd. for $C_{10}H_{17}O$ $[M+H]^+$: 153.1279, Found: 153.1278.

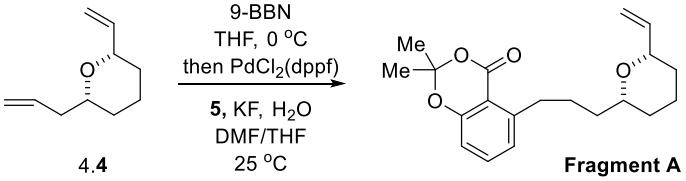
FTIR (neat): 3075, 2935, 2844, 1642, 1434, 1200, 1083, 1046, 994, 914, 696 cm^{-1}.

$[\alpha]^{20}_D$ = -4.70 ° (c 1.0, $CHCl_3$).


f1 (ppm)


139.71
135.24
116.61
114.50
78.43
77.41
41.17
31.54
30.88
23.60
f1 (ppm)

2,2-dimethyl-5-(3-((2*S*,6*S*)-6-vinyltetrahydro-2*H*-pyran-2-yl)propyl)-4*H*-benzo[d][1,3]dioxin-4-one (Fragment A)



A flask was charged with diene **4.4** (343.0 mg, 2.25 mmol, 100 mol%) and 2.25 mL (1 M) fresh distilled THF. The flask was cooled to 0 °C for 5 min. 9-BBN (5.86 mL, 2.93 mmol, 130 mol%) was added dropwise over 1h. The reaction mixture was stirred at 0 °C for 0.5 h, and then gradually warmed to ambient temperature. After 4 h, KF (784.0 mg, 13.5 mmol, 600 mol%), 2,2-dimethyl-4-oxo-4*H*-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate (**5**)[31] (1100.0 mg, 3.375 mmol, 150 mol%), $PdCl_2$(dppf) (82.7 mg, 0.11 mmol, 5 mol%) and H_2O (486.0 mg, 27.0 mmol, 1200 mol%) in 9.0 mL DMF was added to the reaction mixture. The resulting solution was stirred at ambient temperature for 16 h. EtOAc and H_2O (25 mL : 25 mL) were added to the reaction mixture. The organic layer was washed with 25 mL H_2O three times. Dried with Na_2SO_4, and concentrated under vacuo. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 50:1 to 25:1) to furnish the title product **Fragment A** in 55% yield (409.0 mg, 1.24 mmol) with 21% diene **4.4** (72.0 mg, 0.47 mmol) recovered.

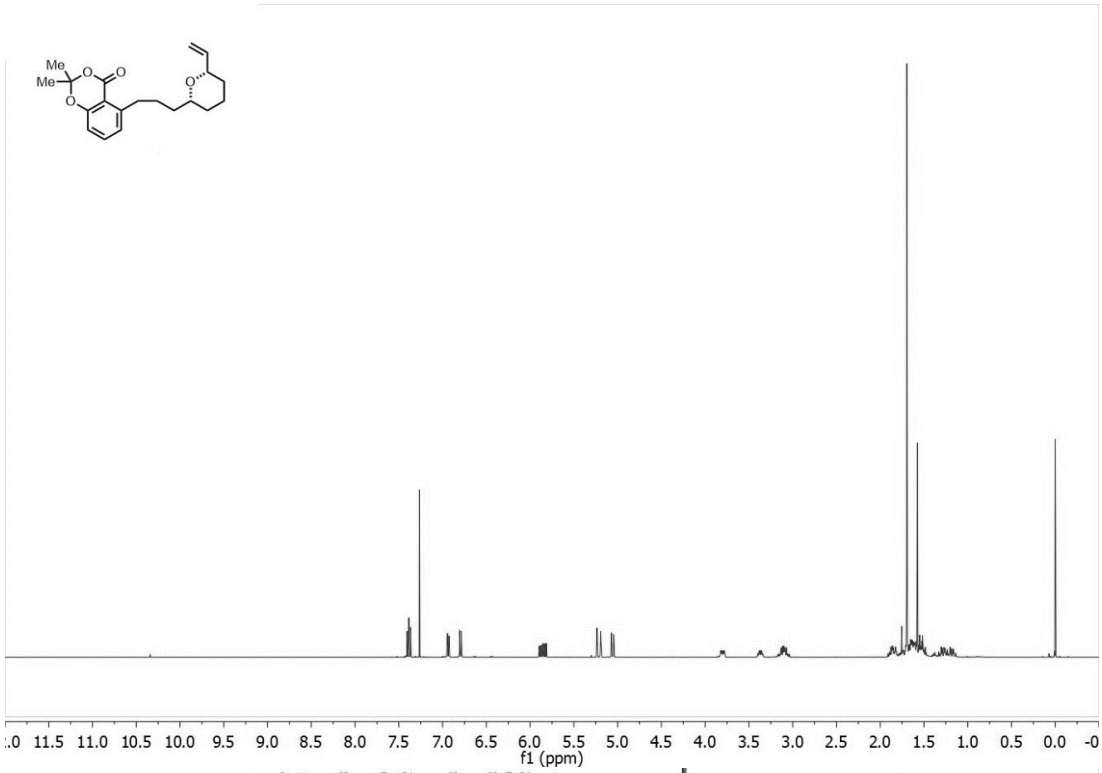
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.2, 7.6 Hz, 1H), 6.94 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.79 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.85 (ddd, *J* = 17.4, 10.6, 5.4 Hz, 1H), 5.22 (dt, *J* = 17.4, 1.7 Hz, 1H), 5.06 (dt, *J* = 10.6, 1.6 Hz, 1H), 3.84–3.76 (m, 1H), 3.41–3.33 (m, 1H), 3.17–3.03 (m, 2H), 1.92–1.80 (m, 1H), 1.79–1.45 (m, 13H), 1.34–1.13 (m, 2H).

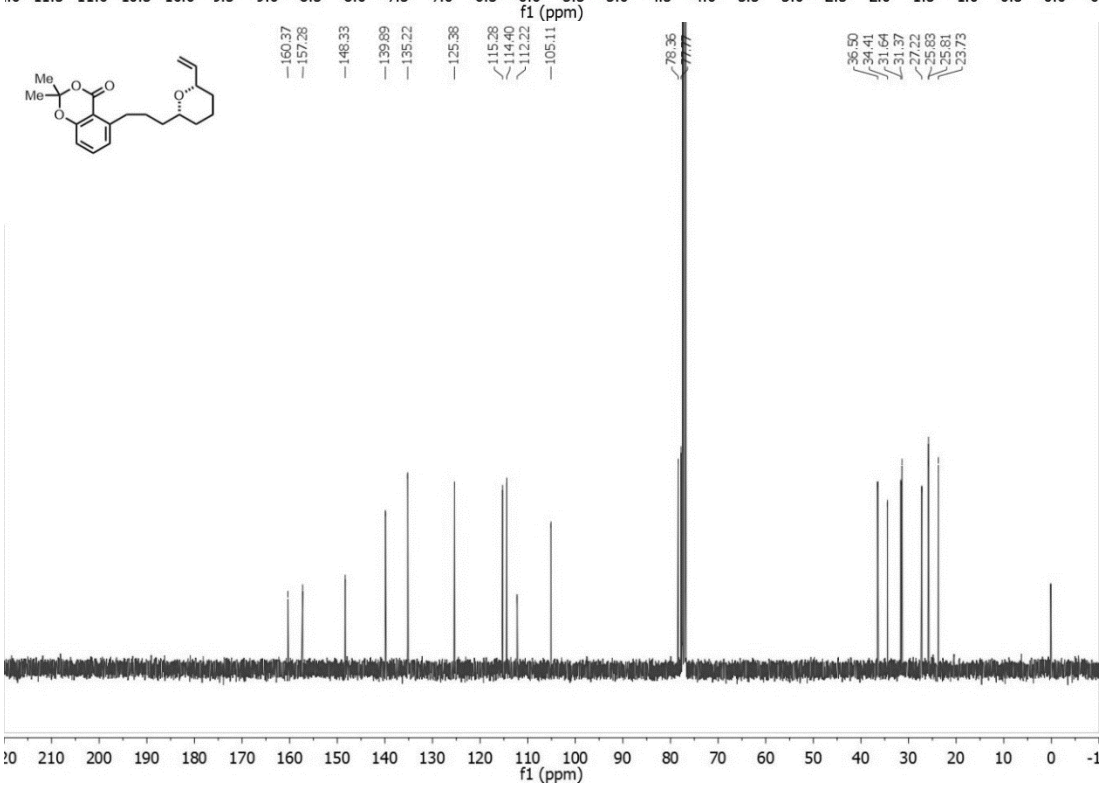
^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 157.3, 148.3, 139.9, 135.2, 125.4, 115.3, 114.4, 112.2, 105.1, 78.4, 77.8, 36.5, 34.4, 31.6, 31.4, 27.2, 25.8, 25.8, 23.7.

HRMS (ESI) Calcd. for $C_{20}H_{26}O_4Na$ $[M+Na]^+$: 353.1723, Found: 353.1729.

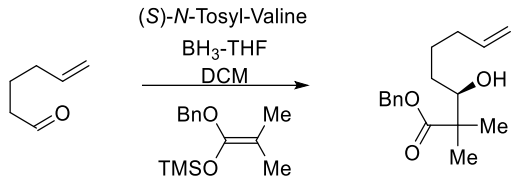
FTIR (neat): 2992, 2932, 2858, 1736, 1695, 1605, 1582, 1476, 1389, 1378, 1313, 1269, 1208, 1074, 1043, 923, 808, 777, 698 cm^{-1}.

$[\alpha]^{20}_D$ = -12.67 ° (c 0.5, $CHCl_3$).


Me
Me
O
O
O
O
f1 (ppm)


Me
Me
O
O
O
O
160.37
157.28
148.33
139.89
135.22
125.38
115.28
114.40
112.22
105.11
78.35
77.77
36.50
34.41
31.64
31.37
27.22
25.83
25.81
23.73
f1 (ppm)

Benzyl (*R*)-3-hydroxy-2,2-dimethyloct-7-enoate (4.7)



4.7

$BH_3 \cdot THF$ (1.0 M in THF, 11.0 mL, 11.0 mmol) was added dropwise to *N*-tosyl-L-valine[31] (1 step, 2984.3 mg, 11.0 mmol, 100 mol%) in DCM (0.1 M, 110.0 mL) at room temperature over 30 min. Then a solution of 5-hexenal[32] (1 step, 1080.0 mg, 11.0 mmol, 100 mol%) in DCM (11.0 mL) and ((1-(benzyloxy)-2-methylprop-1-en-1-yl)oxy)trimethylsilane[33] (1 step, 3055.0 mg, 12.2 mmol, 110 mol%) were added to the resulting solution at -78 °C. After stirring for 4 h, the reaction was quenched at -78 °C by addition of a pH 7.0 buffer solution (115 mL). The resulting mixture was extracted with DCM (3 X 77.0 mL), and the combined organic extracts were washed with brine (150 mL) and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1 to 10:1) to furnish the title product **4.7** in 70% yield (2128.0 mg, 7.7 mmol, 93% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.14 (s, 2H), 5.03–4.91 (m, 2H), 3.63 (ddd, *J* = 10.4, 6.9, 1.8 Hz, 1H), 2.37–2.34 (m, 1H), 2.04 (dtt, *J* = 13.3, 6.8, 1.4 Hz, 2H), 1.73–1.64 (m, 1H), 1.47–1.34 (m, 2H), 1.31–1.22 (m, 1H), 1.20 (d, *J* = 2.4 Hz, 6H).

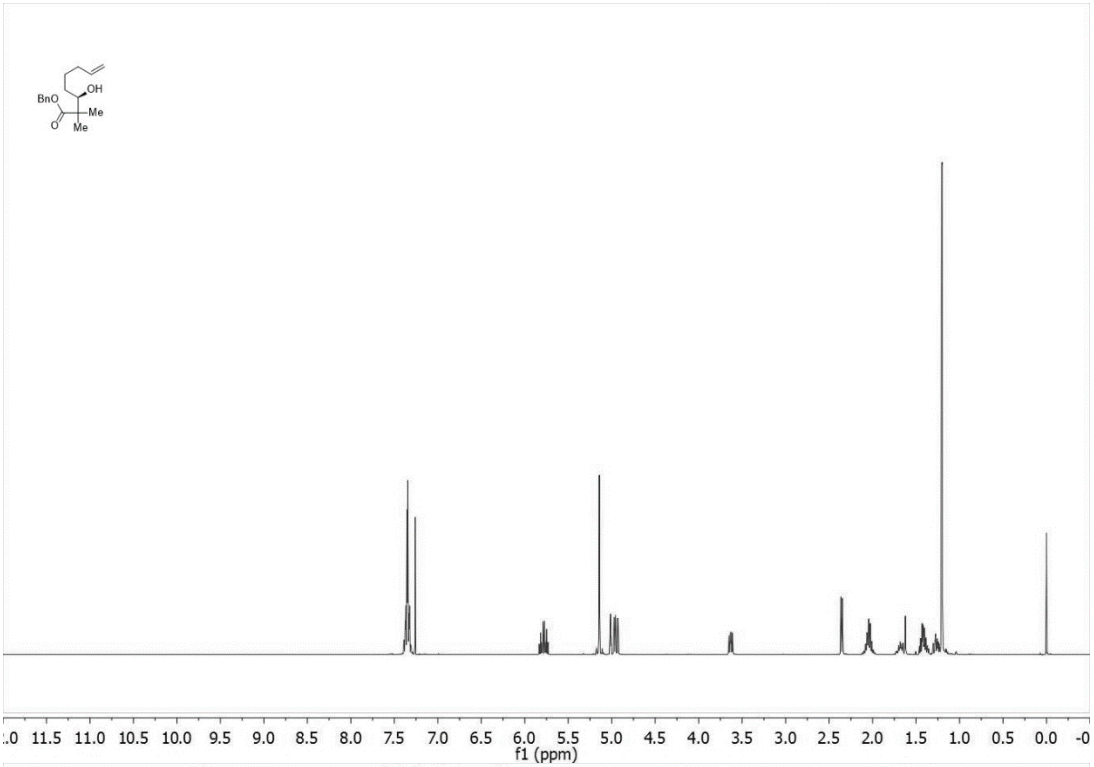
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 138.6, 135.9, 128.6, 128.2, 127.9, 114.6, 76.5, 66.3, 47.3, 33.5, 31.1, 25.9, 22.2, 20.4.

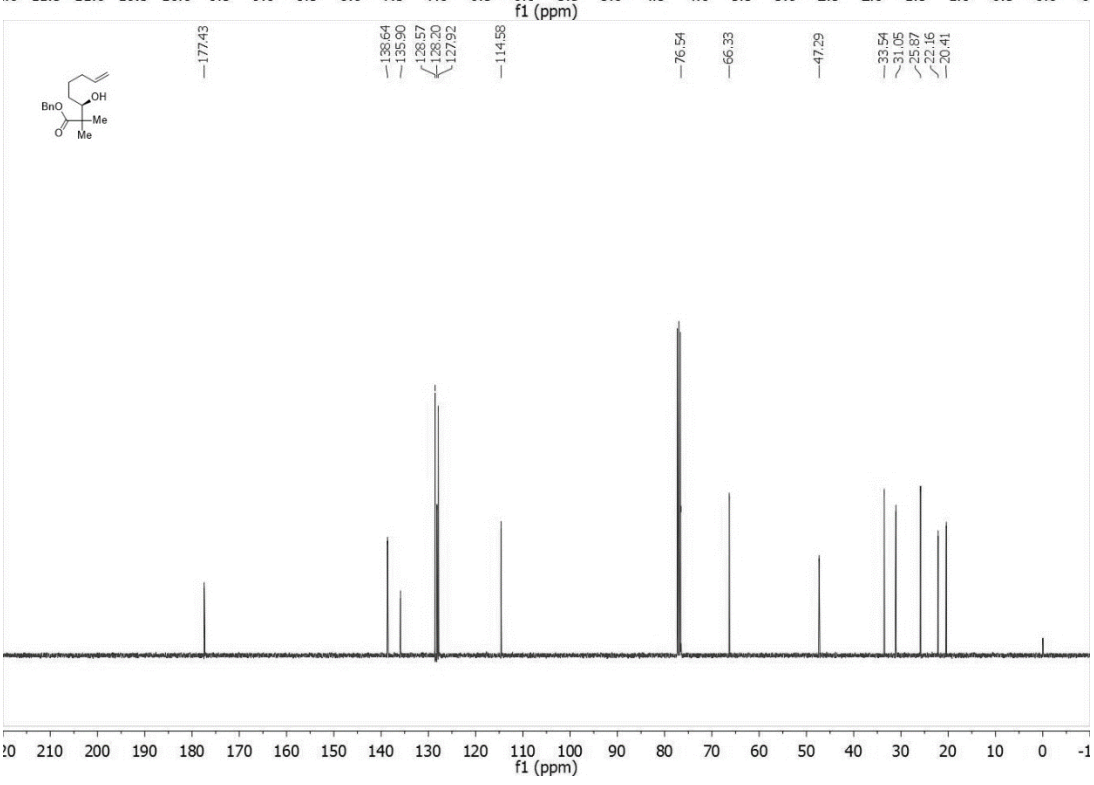
HRMS (ESI) Calcd. for $C_{17}H_{24}O_3Na$ $[M+Na]^+$: 299.1618, Found: 299.1619.

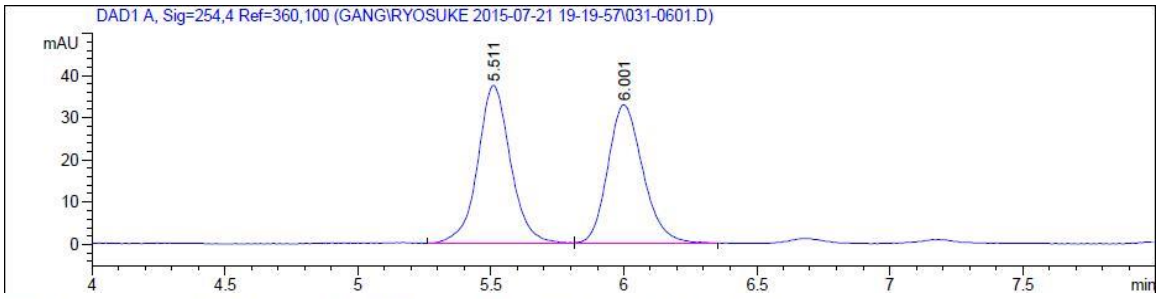
FTIR (neat): 3504, 2976, 2937, 1720, 1455, 1390, 1263, 1213, 1133, 1078, 1029, 993, 969, 911, 750, 697 cm^{-1}.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.00 mL/min, 254 nm), *ee* =93%.

$[\alpha]^{20}_D =$ +11.11 ° (c 0.9, $CHCl_3$).

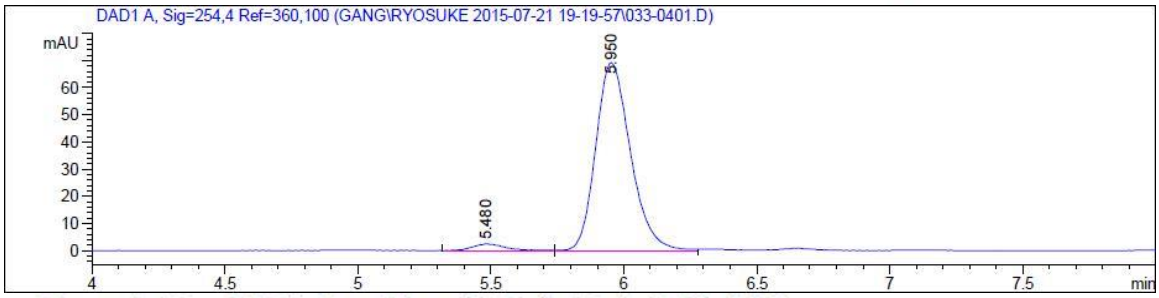

BnO
OH
Me
Me
O
f1 (ppm)


177.43
138.64
135.90
128.57
128.20
127.92
114.58
76.54
66.33
47.29
33.54
31.05
25.87
22.16
20.41
BnO
OH
Me
Me
O
f1 (ppm)



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

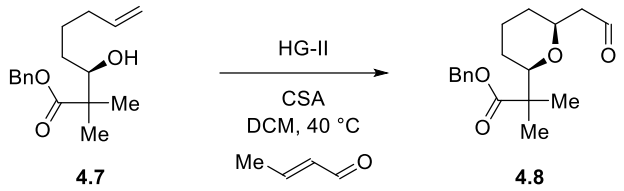
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.511	BV	0.1334	326.93433	37.60009	51.5288
2	6.001	VB	0.1406	307.53488	33.03806	48.4712
Totals :				634.46921	70.63815	



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.480	VV	0.1149	22.31137	2.53014	3.4254
2	5.950	VV	0.1401	629.04224	69.19113	96.5746
Totals :				651.35360	71.72127	

Benzyl 2-methyl-2-((2*R*,6*S*)-6-(2-oxoethyl)tetrahydro-2*H*-pyran-2-yl)propanoate (4.8)



A flame dried flask was charged Hoveyda-Grubbs' 2nd catalyst (551.4 mg, 0.88 mmol, 10 mol%) and (*S*)-camphorsulfonic acid (204.3 mg, 0.88 mmol, 10 mol%). The flask was sealed with a septum and purged with Ar, then freshly distilled CH_2Cl_2 (0.2 M, 44 mL) was added. Alcohol **4.7** (2432 mg, 8.8 mmol, 100 mol%) and crotonaldehyde (2467 mg, 35.2 mmol, 400 mol%) were added. The resulting mixture was stirred at 35 °C for 10 h. The crude mixture was cooled down to ambient temperature, concentrated under vacuo. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1 to 10:1) to furnish the title product **4.8** in 85% yield (2277.0 mg, 7.48 mmol, >20:1 *dr*).

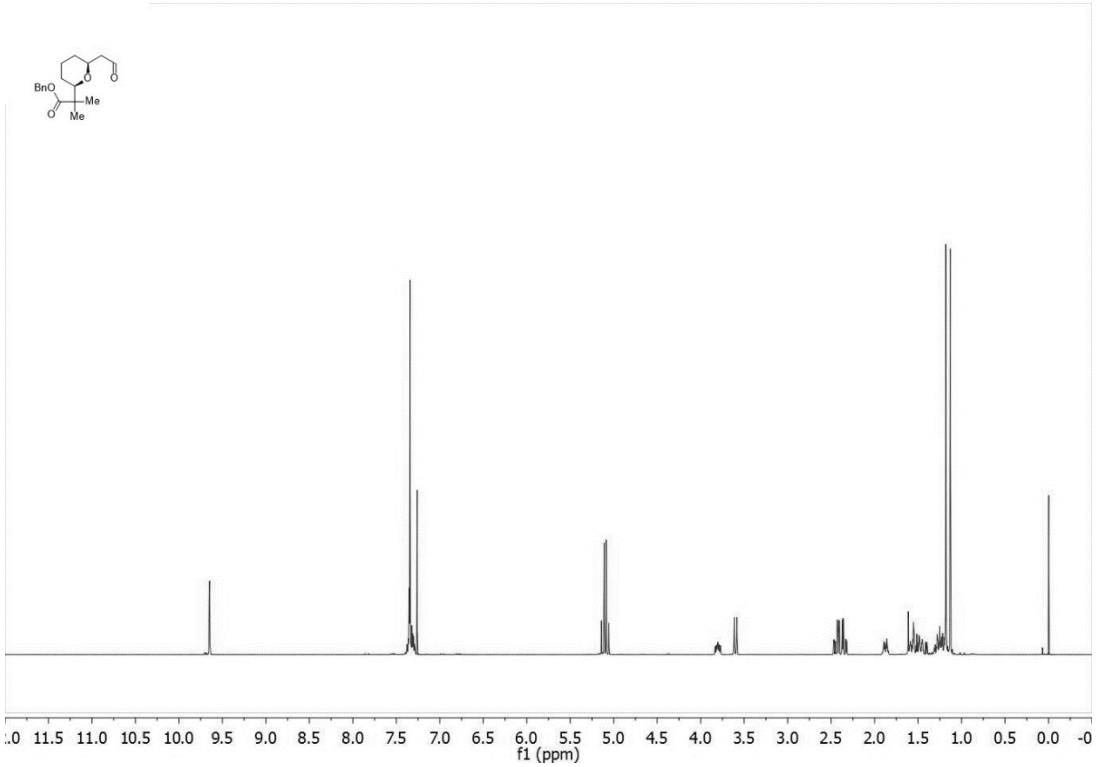
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (dd, *J* = 2.7, 2.0 Hz, 1H), 7.40–7.26 (m, 5H), 5.13 (d, *J* = 12.6 Hz, 1H), 5.07 (d, *J* = 12.6 Hz, 1H), 3.84–3.76 (m, 1H), 3.60 (dd, *J* = 11.4, 1.9 Hz, 1H), 2.48–2.31 (m, 2H), 1.92–1.83 (m, 1H), 1.60–1.43 (m, 3H), 1.32–1.19 (m, 2H), 1.18 (s, 3H), 1.13 (s, 3H).

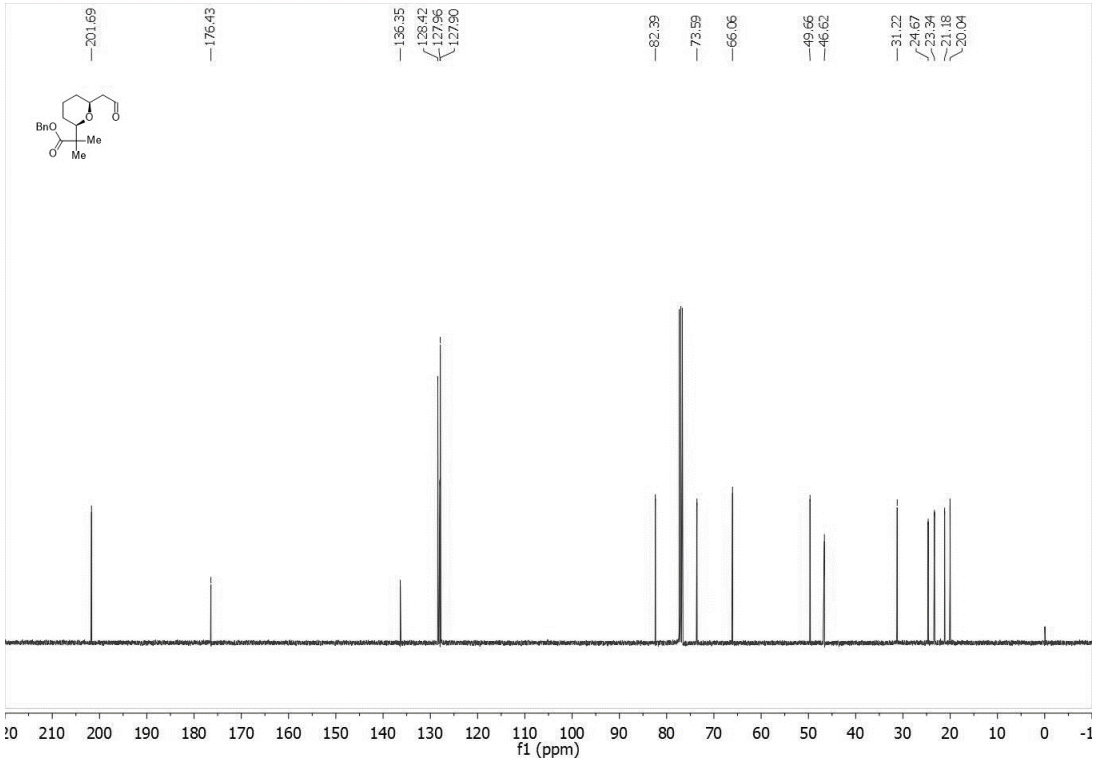
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 176.4, 136.4, 128.4, 128.0, 127.9, 82.4, 73.6, 66.1, 49.7, 46.6, 31.2, 24.7, 23.3, 21.2, 20.0.

HRMS (ESI) Calcd. for $C_{18}H_{24}O_4Na$ $[M+Na]^+$: 327.1567, Found: 327.1576.

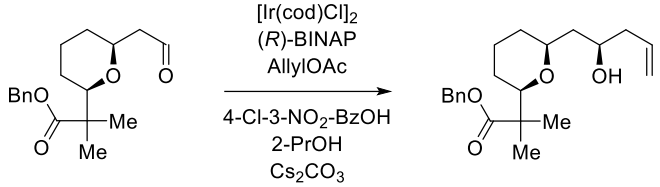
FTIR (neat): 2940, 2860,1727, 1497, 1455, 1391, 1265, 1134, 1085, 1048, 976, 749, 697 cm^{-1}.

$[\alpha]^{20}_D$ = -3.30° (c 1.0, $CHCl_3$).


BnO
O
Me
Me
O
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


201.69
176.43
136.35
128.42
127.96
127.90
82.39
73.59
66.06
49.66
46.62
31.22
24.67
23.34
21.18
20.04
BnO
O
Me
Me
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Benzyl 2-((2*R*,6*S*)-6-((*R*)-2-hydroxypent-4-en-1-yl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (4.9)



4.8 **4.9**

To a sealed tube under an argon atmosphere charged with aldehyde **4.8** (304.4 mg, 1.00 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (16.8 mg, 0.025 mmol, 2.5 mol%), (*R*)-BINAP (31.1 mg, 0.05 mmol, 5.0 mol%), 2-PrOH (180.3 mg, 3.00 mmol, 300 mol%), Cs_2CO_3 (65.1 mg, 0.20 mmol, 20 mol%) and 4-Cl-3-NO_2-BzOH (20.16 mg, 0.10 mmol, 10 mol%) was added freshly distilled THF (5.0 mL, 0.2 M) and allyl acetate (200.2 mg, 2.00 mmol, 200 mol%). The reaction mixture was allowed to stir under microwave condition at 100 °C for 6 h. The reaction mixture was allowed to cool to ambient temperature, and was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 15:1 to 8:1) to furnish the title product **4.9** in 82% yield (284.1 mg, 0.82 mmol, >20:1 *dr*).

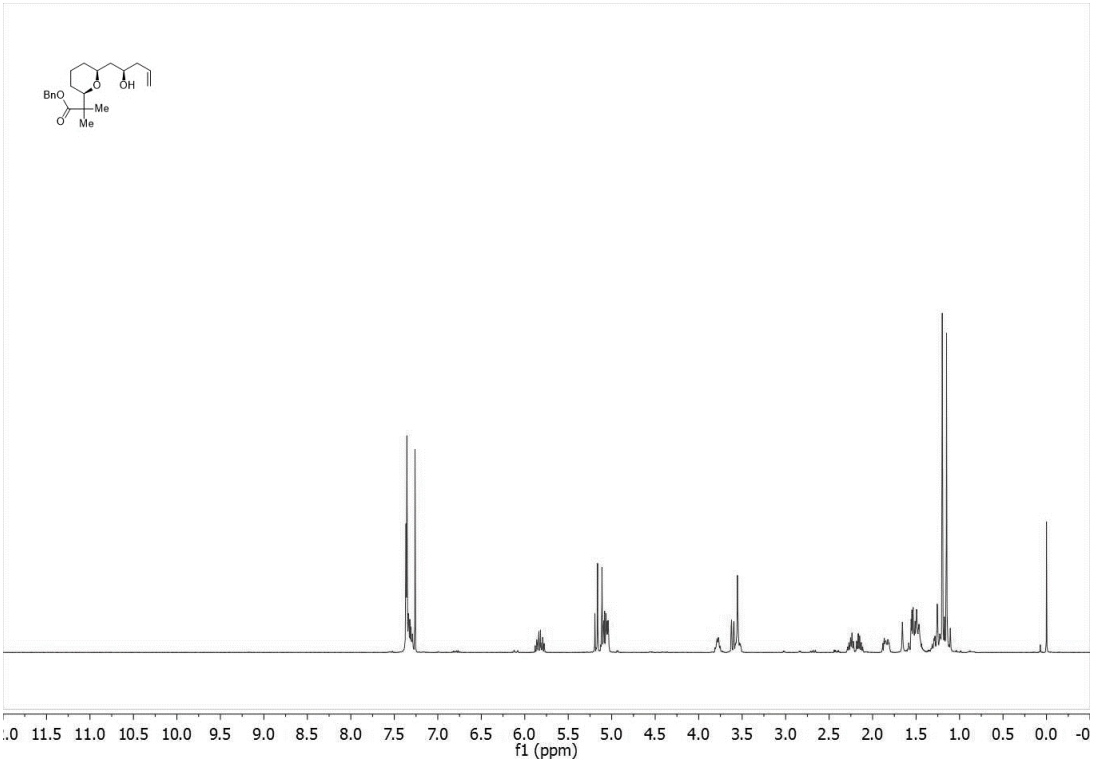
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.83 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.21–5.02 (m, 4H), 3.82–3.74 (m, 1H), 3.61 (dd, *J* = 11.3, 1.8 Hz, 1H), 3.58–3.51 (m, 2H), 2.30–2.21 (m, 1H), 2.19–2.11 (m, 1H), 1.89–1.79 (m, 1H), 1.60–1.43 (m, 5H), 1.33–1.21 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H).

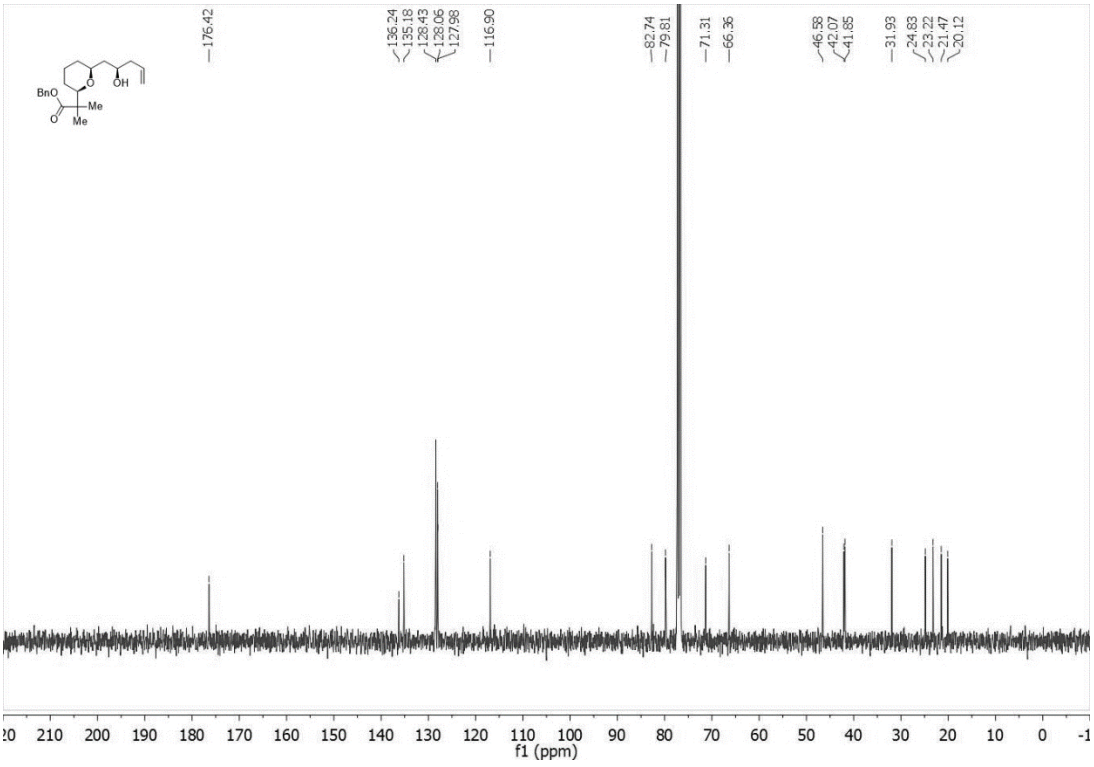
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 136.2, 135.2, 128.4, 128.1, 128.0, 116.9, 82.7, 79.8, 71.3, 66.4, 46.6, 42.1, 41.9, 31.9, 24.8, 23.2, 21.5, 20.1.

HRMS (ESI) Calcd. for $C_{21}H_{30}O_4Na$ $[M+Na]^+$: 369.2036, Found: 369.2043.

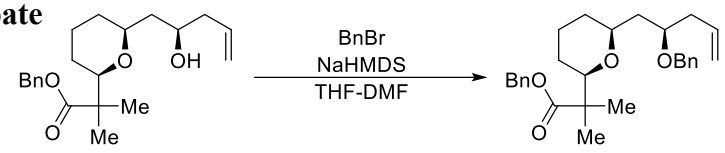
FTIR (neat): 2936, 2860, 1730, 1639, 1455, 1392, 1262, 1140, 1084, 1045, 914, 750, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +2.00° (c 1.0, $CHCl_3$).


BnO
O
Me
Me
OH
f1 (ppm)


176.42
136.24
135.18
128.43
128.06
127.98
116.90
82.74
79.81
71.31
66.36
46.58
42.07
41.85
31.93
24.83
23.22
21.47
20.12
BnO
O
Me
Me
OH
f1 (ppm)

Benzyl 2-((2*R*,6*S*)-6-((*R*)-2-(benzyloxy)pent-4-en-1-yl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate



4.9

A flame dried flask was charged with alcohol **4.9** (2222.2 mg, 6.41 mmol, 100 mol%) in THF (74.0 mL) and DMF (18.5 mL) at 0 °C. BnBr (1645.3 mg, 9.62 mmol, 150 mol%) was added to the solution followed by NaHMDS (1.0 M in THF, 10.3 mL, 10.3 mmol, 160 mol%) at 0 °C. The reaction mixture was warmed to room temperature. After 12 h, the reaction was quenched with 1 N HCl solution (100 mL), and the aqueous layer was extracted with ether (3 X 100 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, filtered and was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 60:1 to 30:1) to furnish the title product in 90% yield (2518.7 mg, 5.77 mmol).

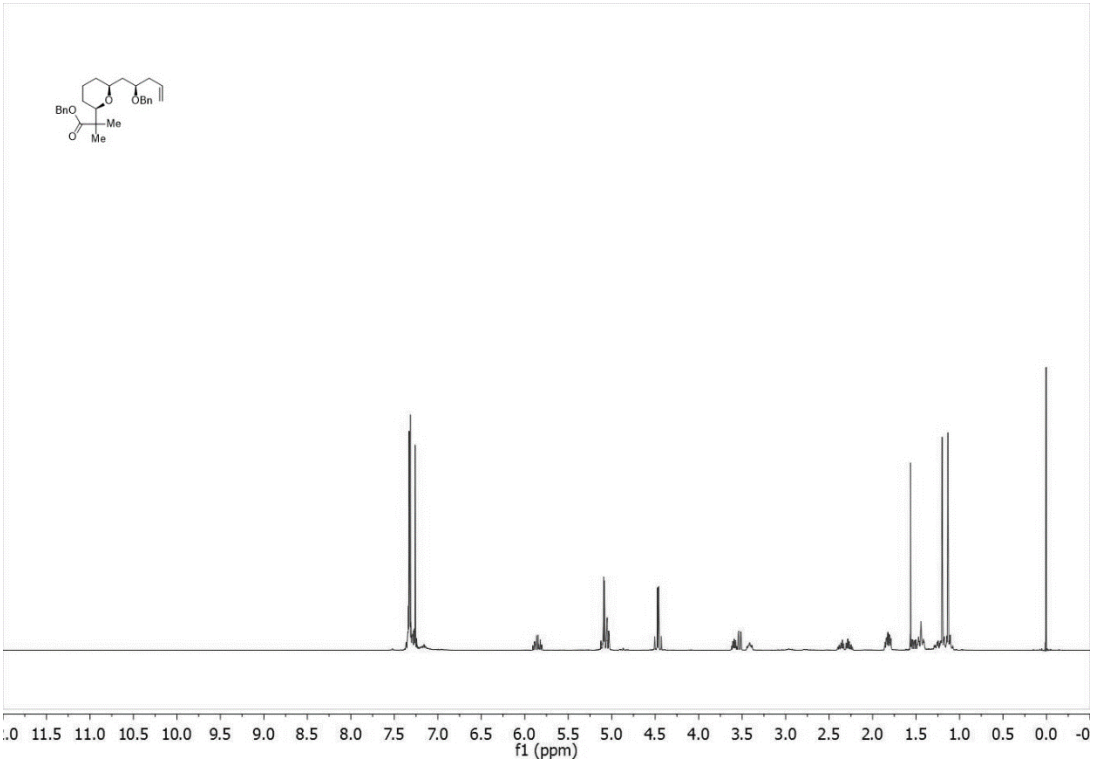
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 10H), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.13–5.02 (m, 4H), 4.47 (dd, *J* = 11.7 Hz, 2H), 3.62–3.56 (m, 1H), 3.53 (dd, *J* = 11.3, 1.8 Hz, 1H), 3.45–3.38 (m, 1H), 2.41–2.32 (m, 1H), 2.31–2.22 (m, 1H), 1.88–1.77 (m, 2H), 1.58–1.50 (m, 1H), 1.49–1.39 (m, 3H), 1.30–1.21 (m, 2H), 1.20 (s, 3H), 1.13 (s, 3H).

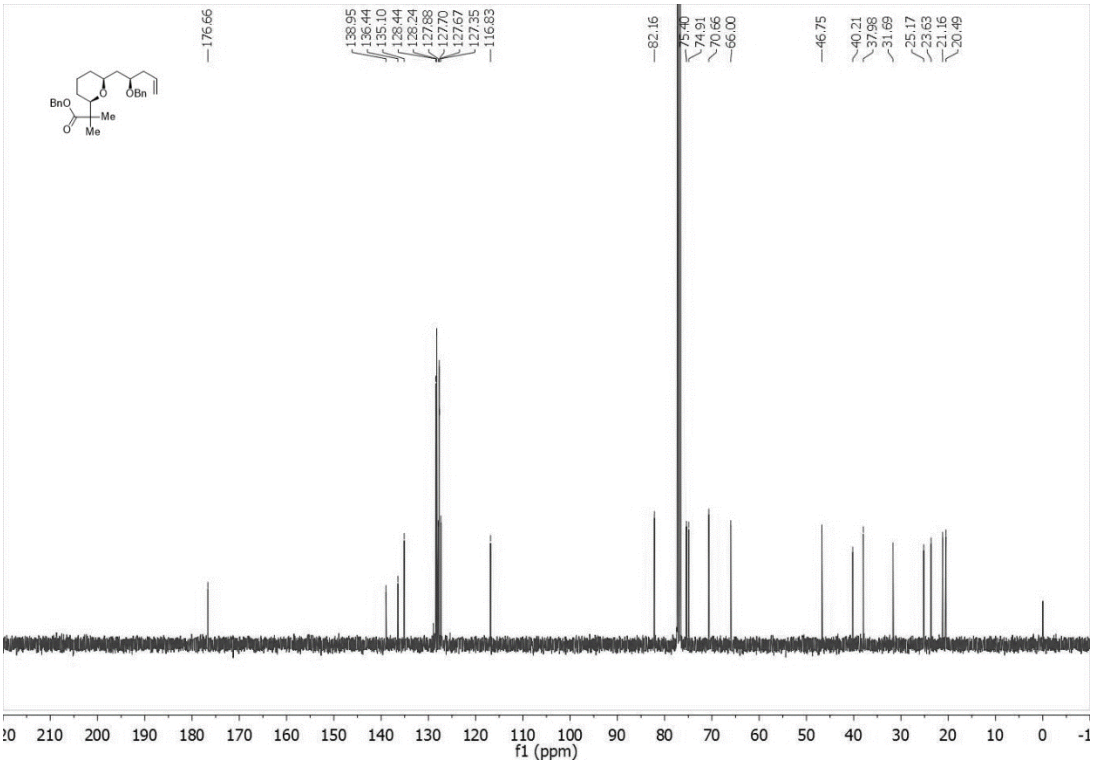
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 138.9, 136.4, 135.1, 128.4, 128.2, 127.9, 127.7, 127.7, 127.4, 116.8, 82.2, 75.4, 74.9, 70.7, 66.0, 46.8, 40.2, 38.0, 31.7, 25.2, 23.6, 21.2, 20.5.

HRMS (ESI) Calcd. for $C_{28}H_{36}O_4Na$ $[M+Na]^+$: 459.2506, Found: 459.2511.

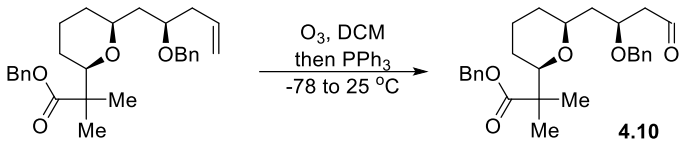
FTIR (neat): 2931, 2858, 2322, 1731, 1640, 1454, 1264, 1134, 1088, 1047, 911, 796, 735, 696, 669 cm^{-1}.

$[\alpha]^{20}_D$ = -20.00° (c 0.4, $CHCl_3$).


BnO
OBn
Me
Me
O
f1 (ppm)


176.66
138.95
136.44
135.10
128.44
128.24
127.88
127.70
127.67
127.35
116.83
82.16
75.40
74.91
70.66
66.00
46.75
40.21
37.98
31.69
25.17
23.63
21.16
20.49
BnO
OBn
Me
Me
O
f1 (ppm)

Benzyl 2-((2*R*,6*S*)-6-((*S*)-2-(benzyloxy)-4-oxobutyl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (4.10)



A flask was charged with alkene (2310.0 mg, 5.29 mmol, 100 mol%) and freshly distilled DCM (88.2 mL, 0.06 M) was added at -78 °C. Ozone was bubbled through the solution for about 15 min at -78 °C. Argon was bubbled through the solution to remove the ozone, then PPh_3 (4170.3 mg, 15.9 mmol, 300 mol%) was added to the solution. The reaction mixture was gradually warmed to room temperature and stirred overnight. The solution was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1 to 10:1) to furnish the title product **4.10** in 83% yield (1925.6 mg, 4.39 mmol).

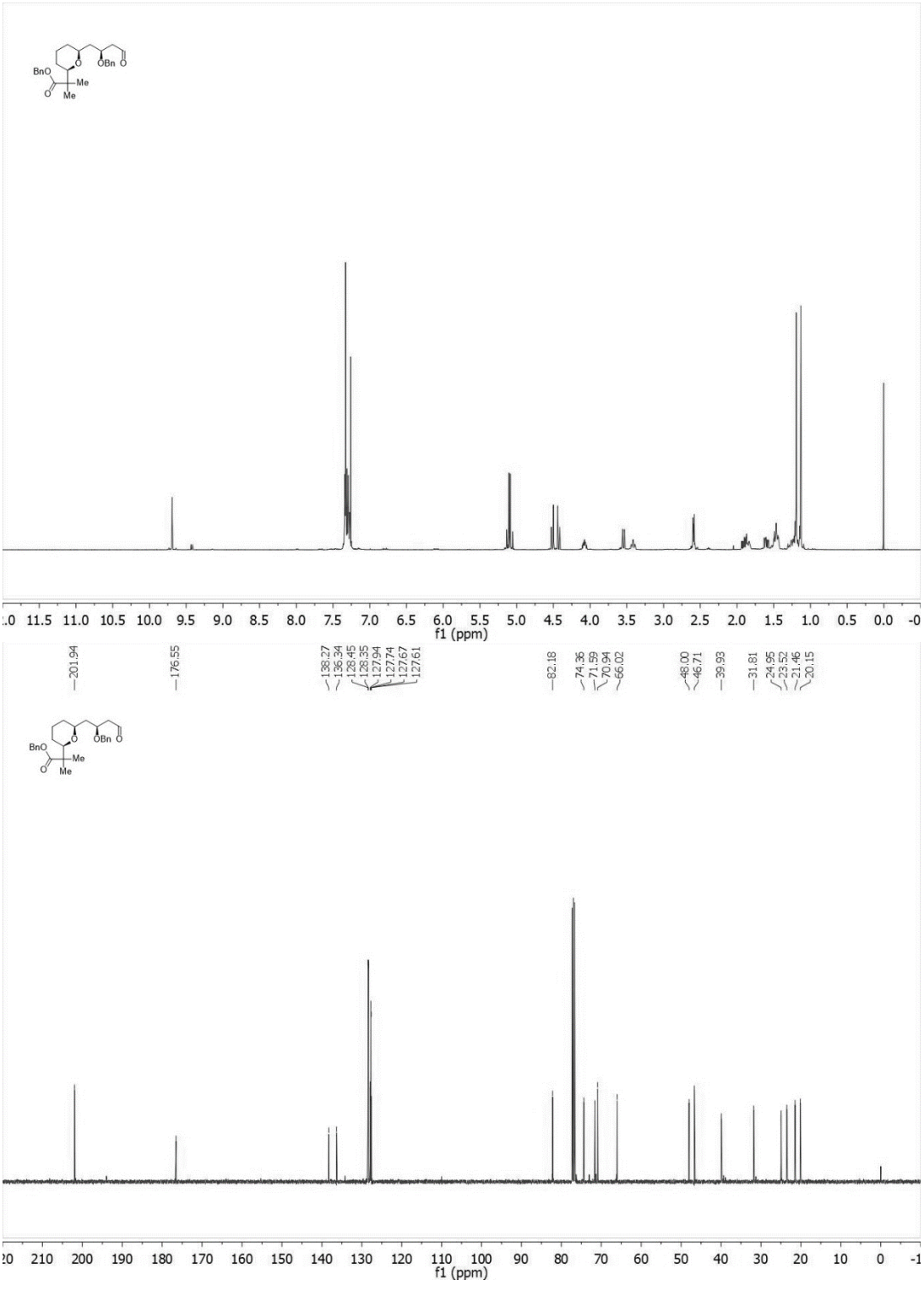
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (t, *J* = 2.2 Hz, 1H), 7.36–7.26 (m, 10H), 5.12 (d, *J* = 12.7 Hz, 1H), 5.07 (d, *J* = 12.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.12–4.03 (m, 1H), 3.55 (dd, *J* = 11.4, 1.8 Hz, 1H), 3.45–3.38 (m, 1H), 2.62–2.56 (m, 2H), 1.95–1.81 (m, 2H), 1.65–1.56 (m, 1H), 1.51–1.42 (m, 3H), 1.32–1.20 (m, 2H), 1.19 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 176.6, 138.3, 136.3, 128.5, 128.4, 127.9, 127.7, 127.7, 127.6, 82.2, 74.4, 71.6, 70.9, 66.0, 48.0, 46.7, 39.9, 31.8, 25.0, 23.5, 21.5, 20.2.

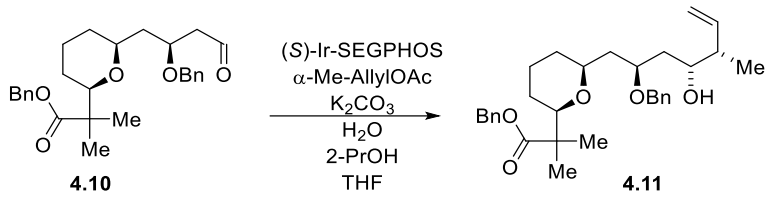
HRMS (ESI) Calcd. for $C_{27}H_{34}O_5Na$ $[M+Na]^+$: 461.2298, Found: 461.2294.

FTIR(neat): 2941, 2860, 1727, 1455, 1391, 1265, 1163, 1138, 1087, 1050, 735, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +8.33° (c 1.0, $CHCl_3$).


BnO
OBn
Me
Me
f1 (ppm)
201.94
176.55
138.27
136.34
128.45
128.35
127.94
127.74
127.67
127.61
82.18
74.36
71.59
70.94
66.02
48.00
46.71
39.93
31.81
24.95
23.52
21.46
20.15
f1 (ppm)

Benzyl 2-((2*R*,6*S*)-6-((2*R*,4*R*,5*S*)-2-(benzyloxy)-4-hydroxy-5-methylhept-6-en-1-yl)tetra-hydro-2*H*-pyran-2-yl)-2-methylpropanoate (4.11)



To a sealed tube under an argon atmosphere charged with aldehyde **4.10** (200.0 mg, 0.46 mmol, 100 mol%), (*S*)-Ir-SEGPHOS (23.5 mg, 0.023 mmol, 5.0 mol%), 2-PrOH (55.3 mg, 0.92 mmol, 200 mol%), K_2CO_3 (31.8 mg, 0.23 mmol, 50 mol%) and H_2O (41.4 mg, 2.30 mmol, 500 mol%) was added freshly distilled THF (0.23 mL, 2.0 M) and α-Me-AllyOAc (105.0 mg, 0.92 mmol, 200 mol%). The septum was quickly replaced with a screw cap and the reaction mixture was allowed to stir in an oil bath at 60 °C for 48 h. The reaction mixture was allowed to cool to ambient temperature, and was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 30:1 to 20:1) to furnish the title product **4.11** in 65% yield (148.0 mg, 0.30 mmol, 12:1 *dr*).

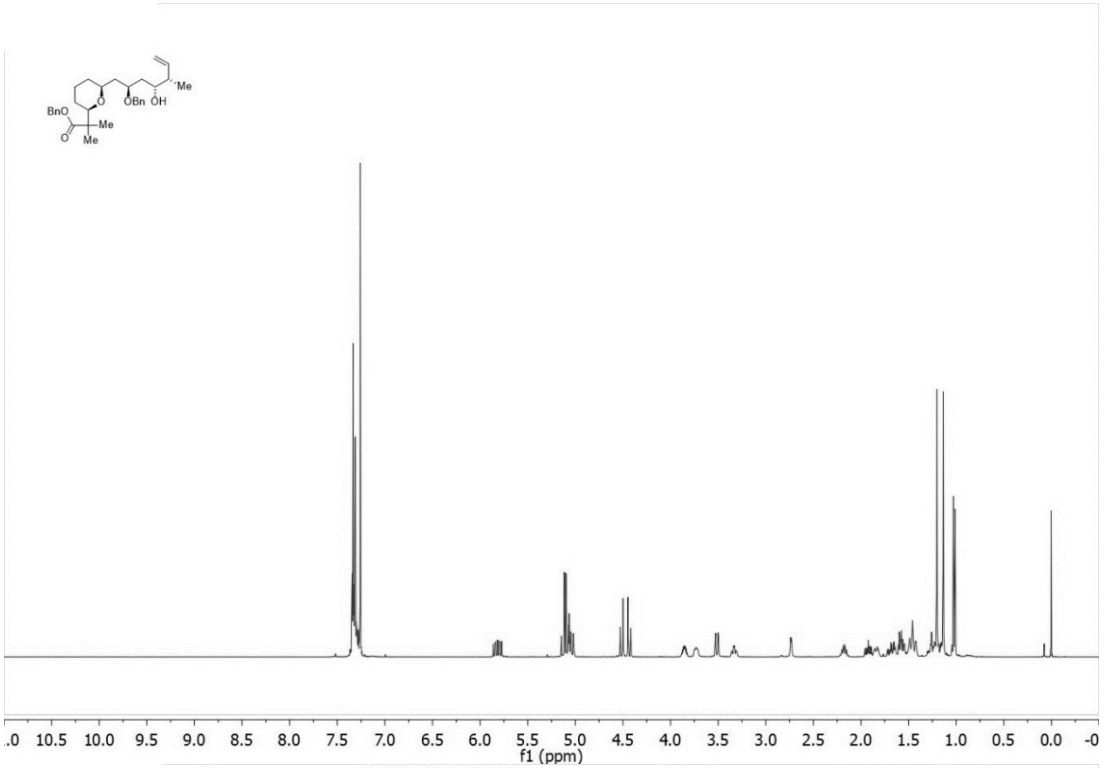
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H), 5.87–5.76 (m, 1H), 5.16–5.00 (m, 4H), 4.54–4.40 (dd, *J* = 12.0, 11.6 Hz 2H), 3.89–3.81 (m, 1H), 3.76–3.69 (m, 1H), 3.51 (dd, *J* = 11.3, 1.8 Hz, 1H), 3.38–3.29 (m, 1H), 2.73 (d, *J* = 3.6 Hz, 1H), 2.23–2.10 (m, 1H), 1.97–1.78 (m, 2H), 1.73–1.39 (m, 6H), 1.32–1.10 (m, 8H), 1.02 (d, *J* = 6.9 Hz, 3H).

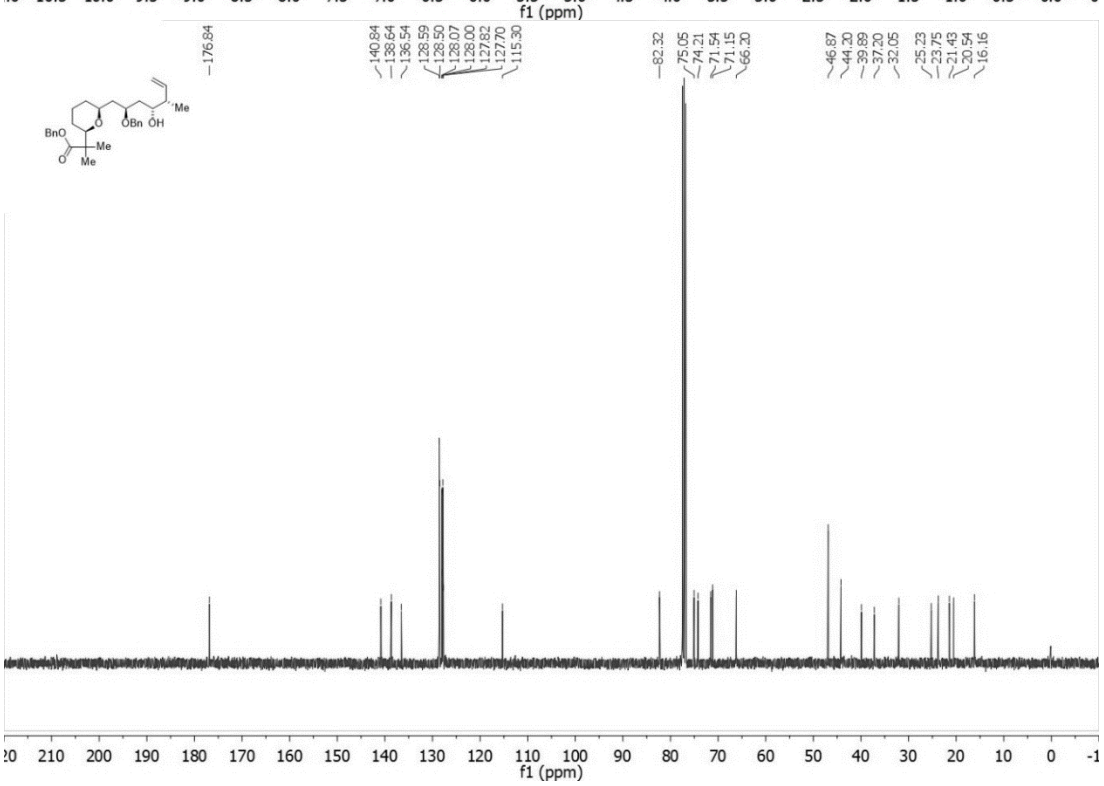
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 140.8, 138.6, 136.5, 128.6, 128.5, 128.1, 128.0, 127.8, 127.7, 115.3, 82.3, 75.1, 74.2, 71.5, 71.2, 66.2, 46.9, 44.2, 39.9, 37.2, 32.1, 25.2, 23.8, 21.4, 20.5, 16.2.

HRMS (ESI) Calcd. for $C_{31}H_{42}O_5Na$ $[M+Na]^+$: 517.2924, Found: 517.2926.

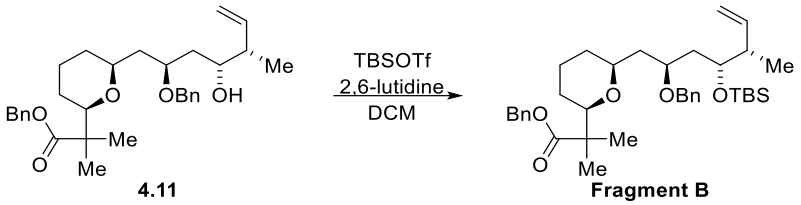
FTIR (neat): 2937, 2858, 2322, 1731, 1496, 1454, 1391, 1265, 1196, 1137, 1087, 1049, 913, 805, 734, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +8.80° (c 2.5, $CHCl_3$).


BnO
OBn
OH
Me
Me
Me
f1 (ppm)


176.84
140.84
138.64
136.54
128.59
128.50
128.07
128.00
127.82
127.70
115.30
82.32
75.05
74.21
71.54
71.15
66.20
46.87
44.20
39.89
37.20
32.05
25.23
23.75
21.43
20.54
16.16
BnO
OBn
OH
Me
Me
Me
f1 (ppm)

Benzyl 2-((2*R*,6*S*)-6-((2*S*,4*R*,5*S*)-2-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-5-methylhept -6-en-1-yl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate



2,6-Lutidine (91.8 mg, 0.856 mmol, 400 mol%) and TBSOTf (113.1mg, 0.428 mmol, 200 mol%) were added to a solution of alcohol **4.11** (106.0 mg, 0.214 mmol, 100 mol%) in DCM (3.6 mL, 0.06 M) at 0 °C. After stirring for 3 h, the reaction mixture was diluted with DCM (4 mL) and washed with sat. NH_4Cl solution (10 mL). The aqueous layer was extracted with DCM (3 X 10 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1) to furnish the title product **Fragment B** in 90% yield (117.3 mg, 0.193 mmol).

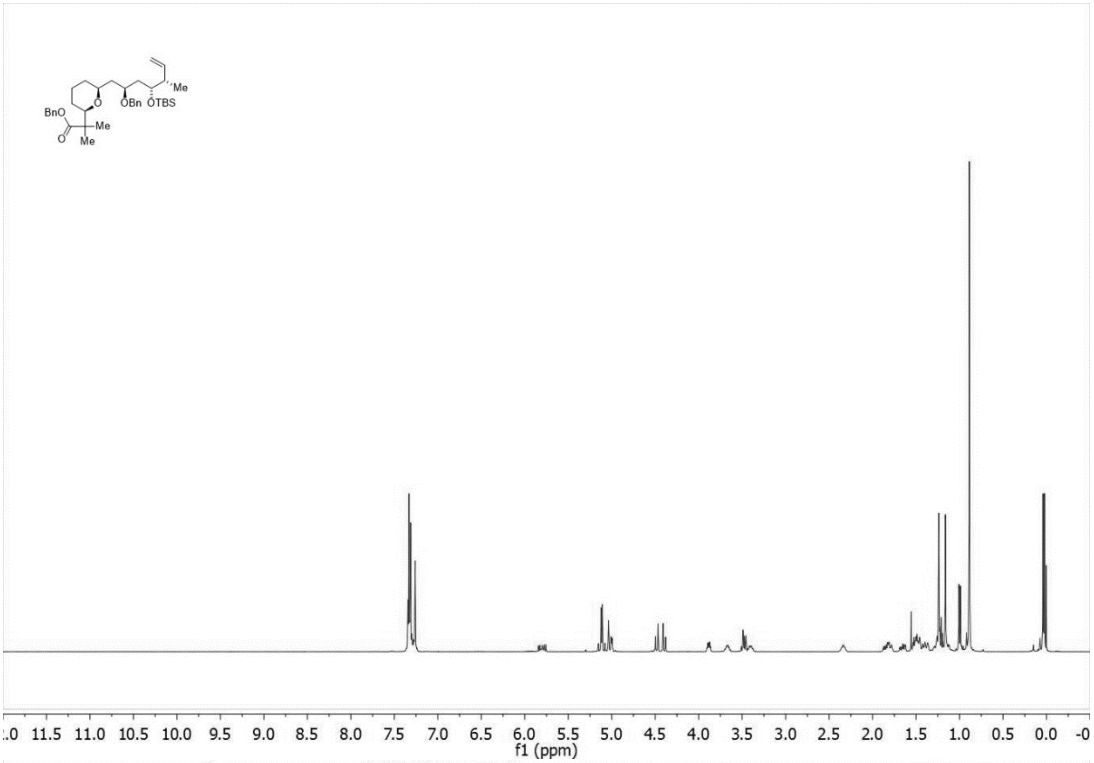
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 10H), 5.86–5.74 (m, 1H), 5.14 (d, *J* = 12.6 Hz, 1H), 5.09 (d, *J* = 12.6 Hz, 1H), 5.05–4.98 (m, 2H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.91–3.85 (m, 1H), 3.71–3.63 (m, 1H), 3.51–3.45 (m, 1H), 3.40 (m, 1H), 2.39–2.30 (m, 1H), 1.90–1.76 (m, 2H), 1.71–1.61 (m, 1H), 1.55–1.35 (m, 5H), 1.31–1.10 (m, 8H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.03 (d, *J* = 6.6 Hz, 6H).

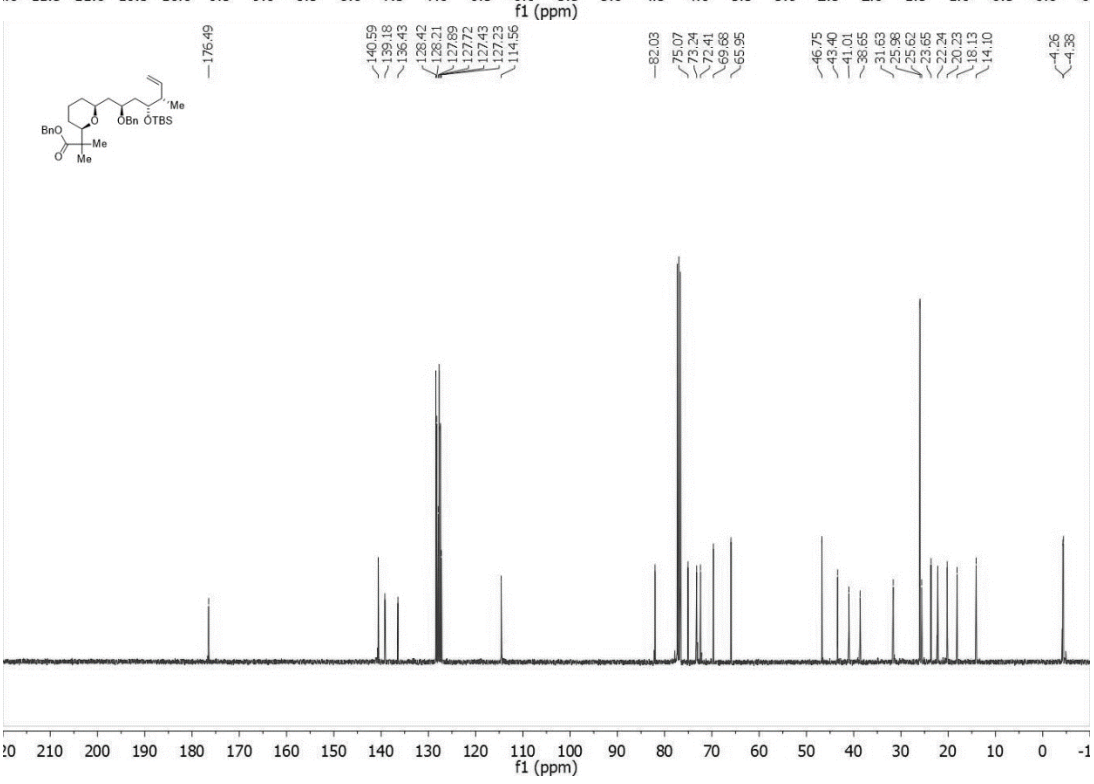
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 140.6, 139.2, 136.4, 128.4, 128.2, 127.9, 127.7, 127.4, 127.2, 114.6, 82.0, 75.1, 73.2, 72.4, 69.7, 66.0, 46.8, 43.4, 41.0, 38.7, 31.6, 26.0, 25.6, 23.7, 22.2, 20.2, 18.1, 14.1, -4.3, -4.4.

HRMS (ESI) Calcd. for $C_{37}H_{56}O_5SiNa$ $[M+Na]^+$: 631.3804, Found: 631.3808.

FTIR (neat): 2930, 2856, 1735, 1471, 1455, 1373, 1316, 1257, 1135, 1088, 1048, 1005, 914, 834, 774, 733, 696 cm^{-1}.

$[\alpha]^{20}_D$ = +8.67° (c 1.0, $CHCl_3$).


BnO
OBn
OTBS
Me
Me
Me
f1 (ppm)


176.49
140.59
139.18
136.43
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128.21
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127.72
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114.56
82.03
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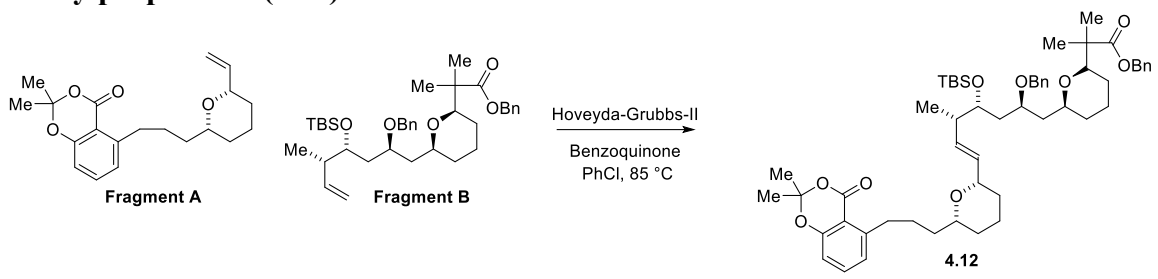
73.24
72.41
69.68
65.95
46.75
43.40
41.01
38.65
31.63
25.98
25.62
23.65
22.24
20.23
18.13
14.10
-4.26
-4.38
BnO
OBn
OTBS
Me
Me
Me
f1 (ppm)

Benzyl 2-((2*S*,6*S*)-6-((2*S*,4*R*,5*S*,*E*)-2-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-7-((2*S*,6*S*)-6-(3-(2,2-dimethyl-4-oxo-4*H*-benzo[d][1,3]dioxin-5-yl)propyl)tetrahydro-2*H*-pyran-2-yl)-5-methylhept-6-en-1-yl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (4.12)



A flame dried flask under an argon atmosphere was charged with fragment **A** (57.0 mg, 0.172 mmol, 150 mol%), fragment **B** (70.0 mg, 0.115 mmol, 100 mol%), 1,4-benzoquinone (1.2 mg, 0.0115 mmol, 10 mol%) and second generation Hoveyda-Grubbs catalyst (7.2 mg, 0.0115 mmol, 10 mol%). C_6H_5Cl (2.90 mL, 0.04 M) was added and the resulting solution was heated at 85 °C for 16 h. The reaction mixture was allowed to cool to ambient temperature, and was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/acetone, 30:1) to furnish the title product **4.12** in 53% yield (55.5 mg, 0.061 mmol, >20:1 *E:Z*).

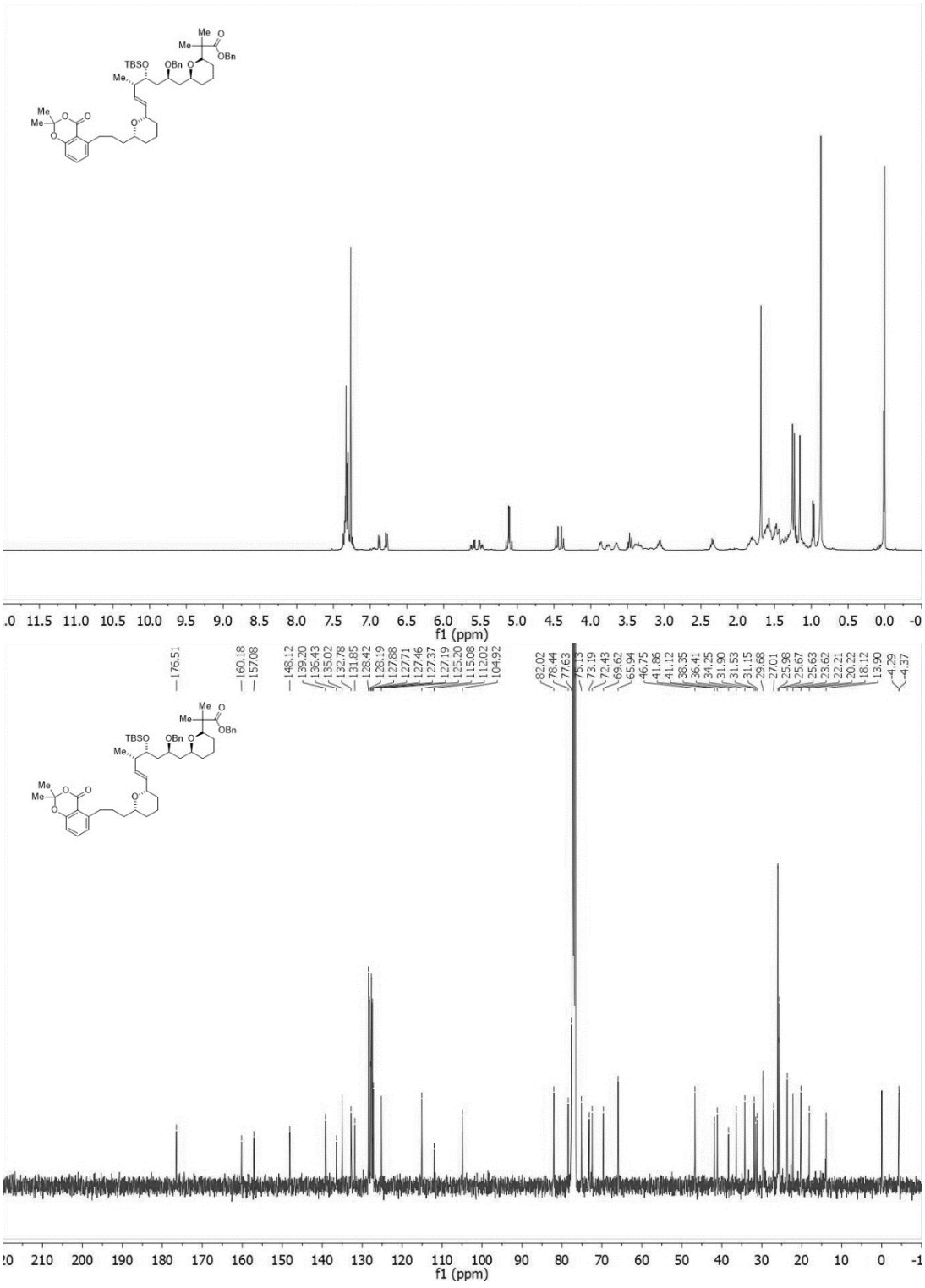
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 11H), 6.87 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.60 (dd, *J* = 15.6, 6.5 Hz, 1H), 5.49 (dd, *J* = 15.7, 6.0 Hz, 1H), 5.16–5.06 (m, 2H), 4.49–4.36 (m, 2H), 3.90–3.83 (m, 1H), 3.80–3.73 (m, 1H), 3.69–3.61 (m, 1H), 3.46 (d, *J* = 10.2 Hz, 1H), 3.42–3.29 (m, 2H), 3.13–2.98 (m, 2H), 2.38–2.29 (m, 1H), 1.89–1.74 (m, 3H), 1.68 (s, 6H), 1.65–1.53 (m, 6H), 1.53–1.34 (m, 7H), 1.32–1.08 (m, 10H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 160.2, 157.1, 148.1, 139.2, 136.4, 135.0, 132.8, 131.9, 128.4, 128.2, 127.9, 127.7, 127.5, 127.4, 127.2, 125.2, 115.1, 112.0, 104.9, 82.0, 78.4, 77.6, 75.1, 73.2, 72.4, 69.6, 65.9, 46.8, 41.9, 41.1, 38.4, 36.4, 34.3, 31.9, 31.5, 31.2, 29.7, 27.0, 26.0, 25.7, 25.6, 23.6, 22.2, 20.2, 18.1, 13.9, -4.3, -4.4.

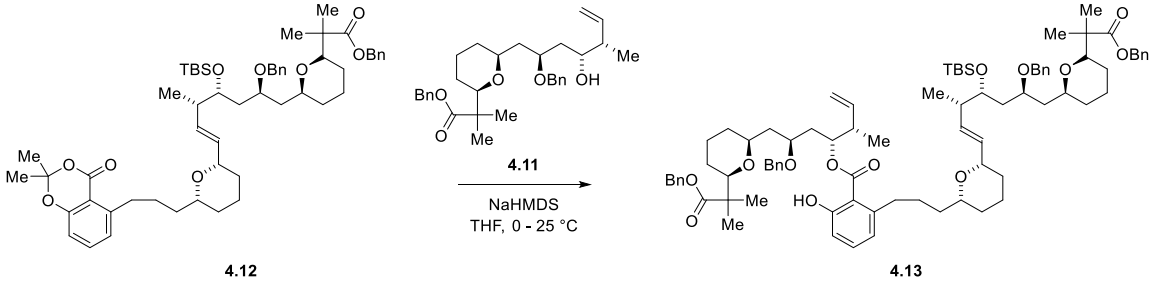
HRMS (ESI) Calcd. for $C_{55}H_{78}O_9SiNa$ $[M+Na]^+$: 933.5307, Found: 933.5309.

FTIR (neat): 2932, 2850, 1737, 1606, 1582, 1478, 1468, 1453, 1388, 1378, 1305, 1271, 1208, 1111, 1072, 1044, 967, 927, 807, 749, 689 cm^{-1}.

$[\alpha]^{20}_D$ = -10.00° (c 0.2, $CHCl_3$).


f1 (ppm)
f1 (ppm)

(3*S*,4*R*,6*S*)-6-(benzyloxy)-7-((2*S*,6*R*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydro -2*H*-pyran-2-yl)-3-methylhept-1-en-4-yl 2-(3-((2*S*,6*S*)-6-((3*S*,4*R*,6*S*,*E*)-6-(benzyloxy)-7-((2*S*, 6*S*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydro-2*H*-pyran-2-yl)-4-((*tert*-butyldi-methylsilyl)oxy)-3-methylhept-1-en-1-yl)tetrahydro-2*H*-pyran-2-yl)propyl)-6-hydroxybenz-oate (4.13)



A flame dried flask under an argon atmosphere was charged with alcohol **4.11** (37.1 mg, 0.0751 mmol, 120 mol%) in THF (1.25 mL, 0.05 M) at 0 °C. NaHMDS (0.313 mL, 0.313 mmol, 500 mol%) was added dropwise at 0 °C. After stirring for 30 min, the alkene **4.12** (57.0 mg, 0.0625 mmol, 100 mol%) in dry THF (0.6 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 1 h and then quenched with sat. NH_4Cl solution (5.0 mL). The resulting mixture was extracted with ether (3 X 5.0 mL). The combined organic extracts were washed with brine (15.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 30:1 to 15:1) to furnish the title product **4.13** in 80% yield (67.4 mg, 0.05 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.35–7.21 (m, 21H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 5.87–5.76 (m, 1H), 5.65–5.57 (m, 2H), 5.55–5.45 (m, 1H), 5.13–5.02 (m, 6H), 4.49–4.28 (m, 4H), 3.91–3.84 (m, 1H), 3.76 (dd, *J* = 10.9, 6.0 Hz, 1H), 3.69–3.63 (m, 1H), 3.60–3.53 (m, 1H), 3.51–3.22 (m, 5H), 2.95–2.78 (m, 2H), 2.58–2.49 (m, 1H), 2.39–2.30 (m, 1H), 1.90–1.74 (m, 7H), 1.70–1.52 (m, 7H), 1.52–1.30 (m, 11H),

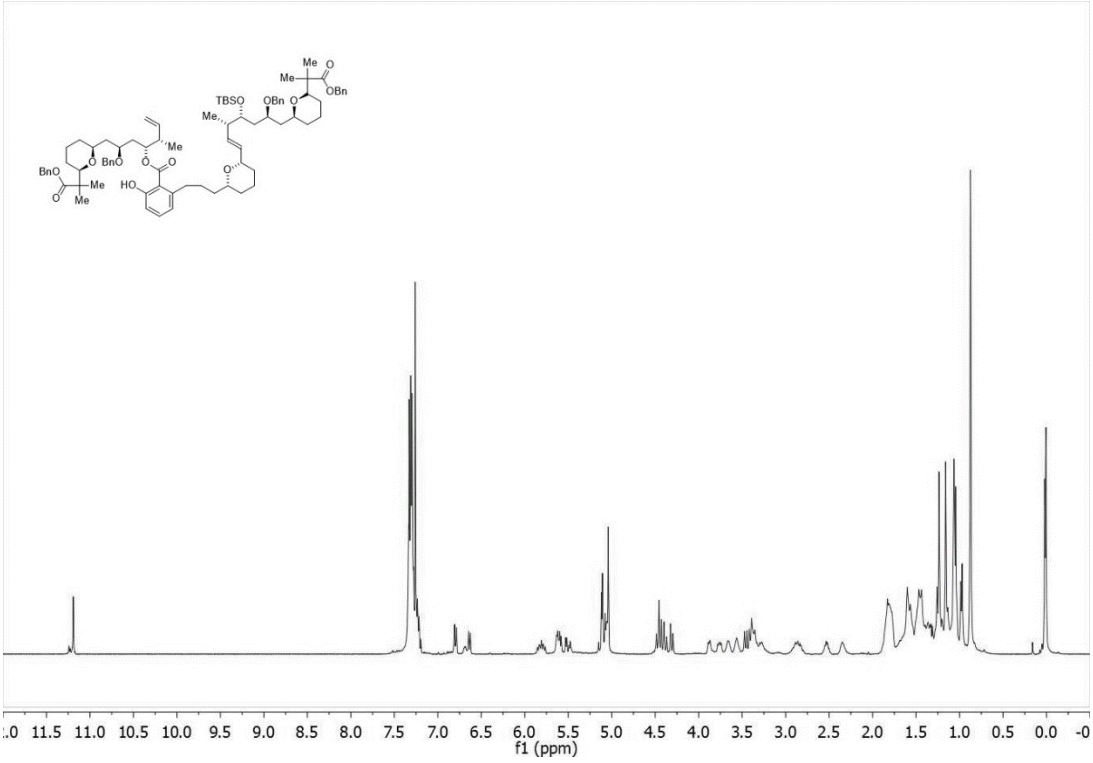
1.23 (s, 6H), 1.16 (d, J = 1.4 Hz, 6H), 1.06 (m, 9H), 1.01–0.95 (m, 2H), 0.88 (s, 9H), 0.01 (s, 6H).

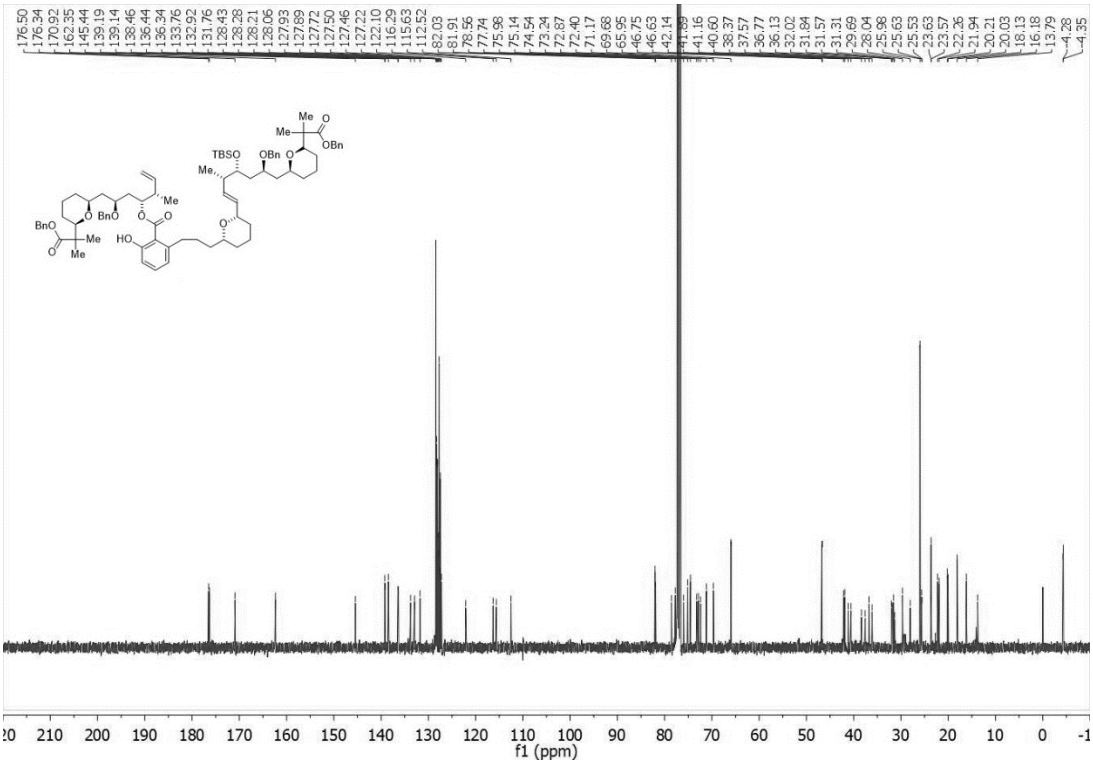
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 176.3, 170.9, 162.4, 145.4, 139.2, 139.1, 138.5, 136.4, 136.3, 133.8, 132.9, 131.8, 128.4, 128.3, 128.2, 128.1, 127.9, 127.9, 127.7, 127.5, 127.5, 127.2, 122.1, 116.3, 115.6, 112.5, 82.0, 81.9, 78.6, 77.7, 76.0, 75.1, 74.5, 73.2, 72.9, 72.4, 71.2, 69.7, 66.0, 46.8, 46.6, 42.1, 41.9, 41.2, 40.6, 38.4, 37.6, 36.8, 36.1, 32.0, 31.8, 31.6, 31.3, 29.7, 28.0, 26.0, 25.6, 25.5, 23.6, 23.6, 22.3, 21.9, 20.2, 20.0, 18.1, 16.2, 13.8, -4.3, -4.4.

HRMS (ESI) Calcd. for $C_{83}H_{114}O_{13}SiNa$ $[M+Na]^+$: 1369.7921, Found: 1369.7918.

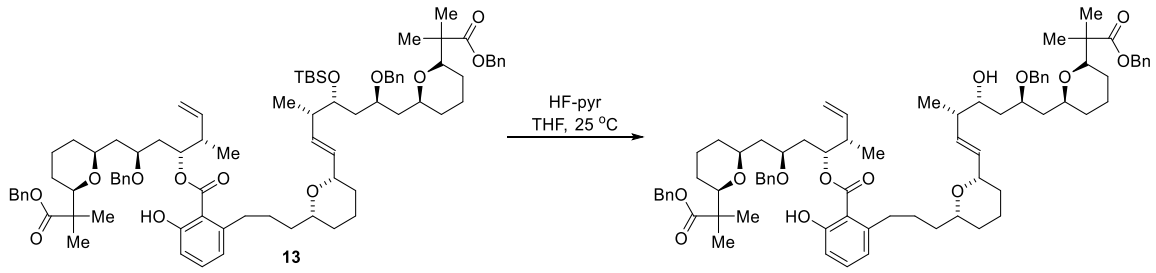
FTIR (neat): 2934, 2856, 1730, 1610, 1549, 1453, 1371, 1251, 1214, 1087, 1048, 1028, 896, 827, 752, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +12.70° (c 0.5, $CHCl_3$).


f1 (ppm)


f1 (ppm)

(3*S*,4*R*,6*S*)-6-(benzyloxy)-7-((2*S*,6*R*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydr-o-2*H*-pyran-2-yl)-3-methylhept-1-en-4-yl 2-(3-((2*S*,6*S*)-6-((3*S*,4*R*,6*R*,*E*)-6-(benzyloxy)-7-((2*S*, 6*S*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydro-2*H*-pyran-2-yl)-4-hydroxy-3-methylhept-1-en-1-yl)tetrahydro-2*H*-pyran-2-yl)propyl)-6-hydroxybenzoate



To a solution of alkene **4.13** (30 mg, 0.022 mmol, 100 mol%) in THF (0.6 mL, 0.037 M) was added HF/Py (0.016 mL, 22.0 mmol, 100000 mol%), and the mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of a sat. $NaHCO_3$ (10 mL), and extracted with ether (3 X 10 mL). The combined organic mixture was dried with Na_2SO_4 and and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 10:1 to 5:1) to furnish the title product in 90% yield (24.7 mg, 0.020 mmol).

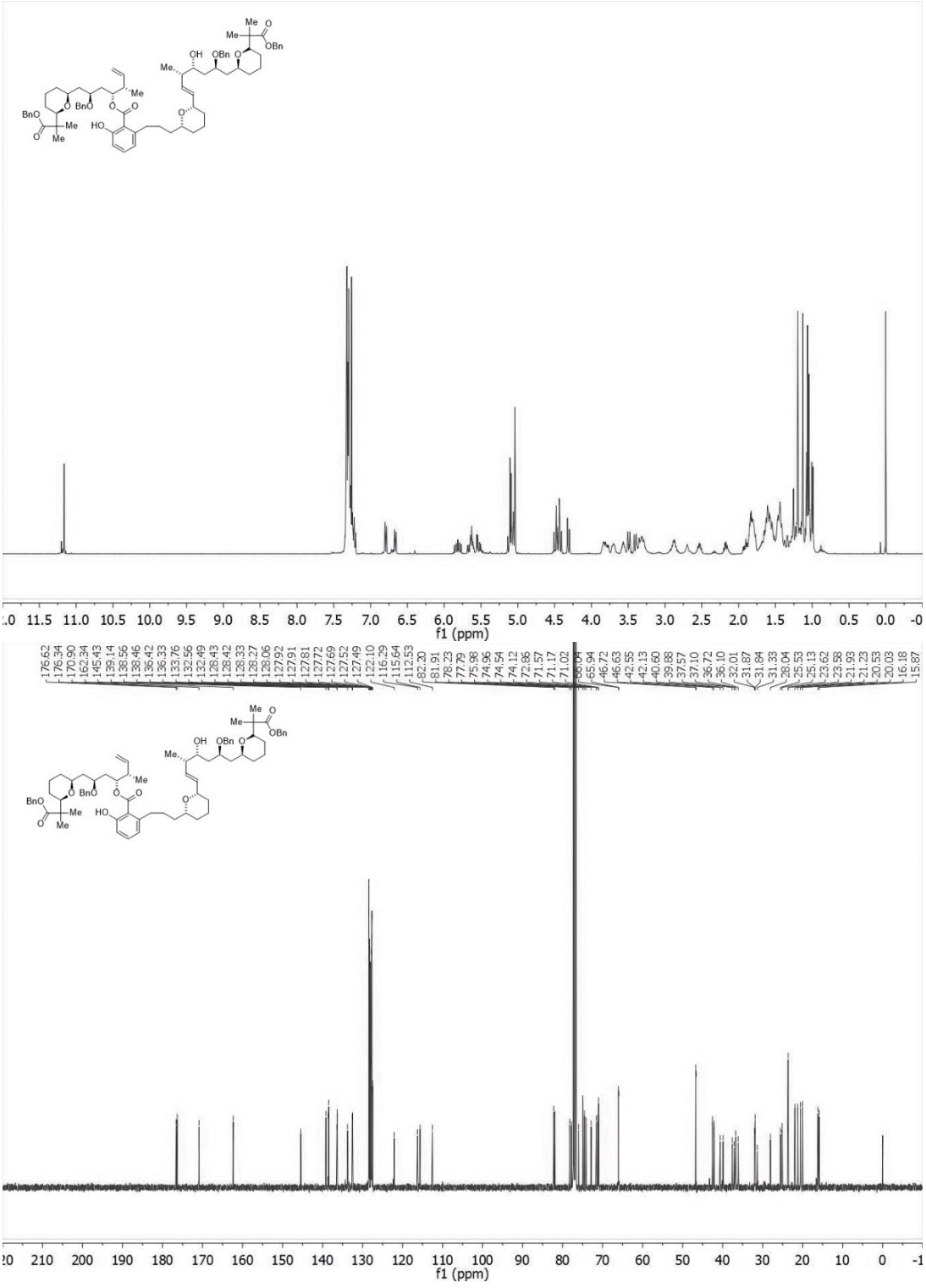
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), 7.36–7.20 (m, 21H), 6.79 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.66 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.89–5.76 (m, 1H), 5.70–5.58 (m, 2H), 5.57–5.49 (m, 1H), 5.14–5.03 (m, 6H), 4.52–4.29 (m, 4H), 3.88–3.75 (m, 2H), 3.74–3.65 (m, 1H), 3.61–3.53 (m, 1H), 3.52–3.46 (m, 1H), 3.43–3.25 (m, 4H), 2.95–2.81 (m, 2H), 2.70 (s, 1H), 2.58–2.49 (m, 1H), 2.22–2.12 (m, 1H), 1.95–1.74 (m, 7H), 1.73–1.50 (m, 10H), 1.50–1.35 (m, 7H), 1.30–1.17 (m, 6H), 1.17–1.11 (m, 6H), 1.11–1.02 (m, 9H), 1.00 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 176.3, 170.9, 162.3, 145.4, 139.1, 138.6, 138.5, 136.4, 136.3, 133.8, 132.6, 132.5, 128.4, 128.4, 128.3, 128.3, 128.1, 127.9, 127.9, 127.8, 127.7, 127.7, 127.5, 127.5, 122.1, 116.3, 115.6, 112.5, 82.2, 81.9, 78.2, 77.8, 76.0, 75.0, 74.5, 74.1, 72.9, 71.6, 71.2, 71.0, 66.0, 65.9, 46.7, 46.6, 42.6, 42.1, 40.6, 39.9, 37.6, 37.1, 36.7, 36.1, 32.0, 31.9, 31.8, 31.3, 28.0, 25.5, 25.1, 23.6, 23.6, 21.9, 21.2, 20.5, 20.0, 16.2, 15.9.

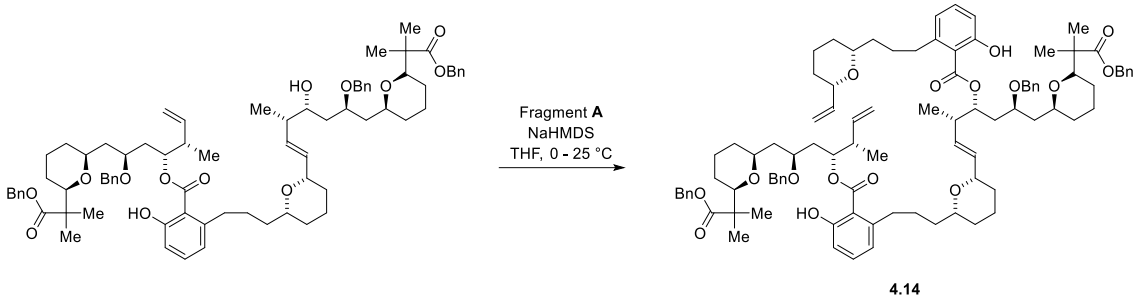
HRMS (ESI) Calcd. for $C_{77}H_{100}O_{13}Na$ $[M+Na]^+$: 1255.7056, Found: 1255.7037.

FTIR (neat): 2931, 2856, 1731, 1652, 1454, 1373, 1311, 1263, 1213, 1163, 1139, 1086, 1048, 1028, 1017, 734, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +6.00° (c 1.0, $CHCl_3$).


f1 (ppm)
f1 (ppm)

(3*S*,4*R*,6*S*)-6-(benzyloxy)-7-((2*S*,6*R*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetra-hydro-2*H*-pyran-2-yl)-3-methylhept-1-en-4-yl 2-(3-((2*S*,6*S*)-6-((3*S*,4*R*,6*S*,*E*)-6-(benzyloxy)-7-((2*S*,6*S*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetrahydro-2*H*-pyran-2-yl)-4-((2-hydroxy-6-(3-((2*S*,6*S*)-6-vinyltetrahydro-2*H*-pyran-2-yl)propyl)benzoyl)oxy)-3-methylhept-1-en-1-yl)tetra-hydro-2*H*-pyran-2-yl)propyl)-6-hydroxybenzoate (4.14)



4.14

A flame dried flask was charged with alcohol (70.0 mg, 0.0567 mmol, 100 mol%) in THF (1.13 mL, 0.05 M) at 0 °C. NaHMDS (0.284 mL, 0.284 mmol, 500 mol%) was added dropwise at 0 °C. After stirring for 30 min, fragment **A** (74.9 mg, 0.227 mmol, 400 mol%) in dry THF (0.6 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 1 h and then quenched with sat. NH_4Cl solution (5.0 mL). The resulting mixture was extracted with ether (3 X 5.0 mL). The combined organic extracts were washed with brine (15.0 mL), dried over Na_2SO_4 and concentrated *in vacuo* and subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1 to 6:1) to furnish the title product **4.14** in 85% yield (72.6 mg, 0.048 mmol).

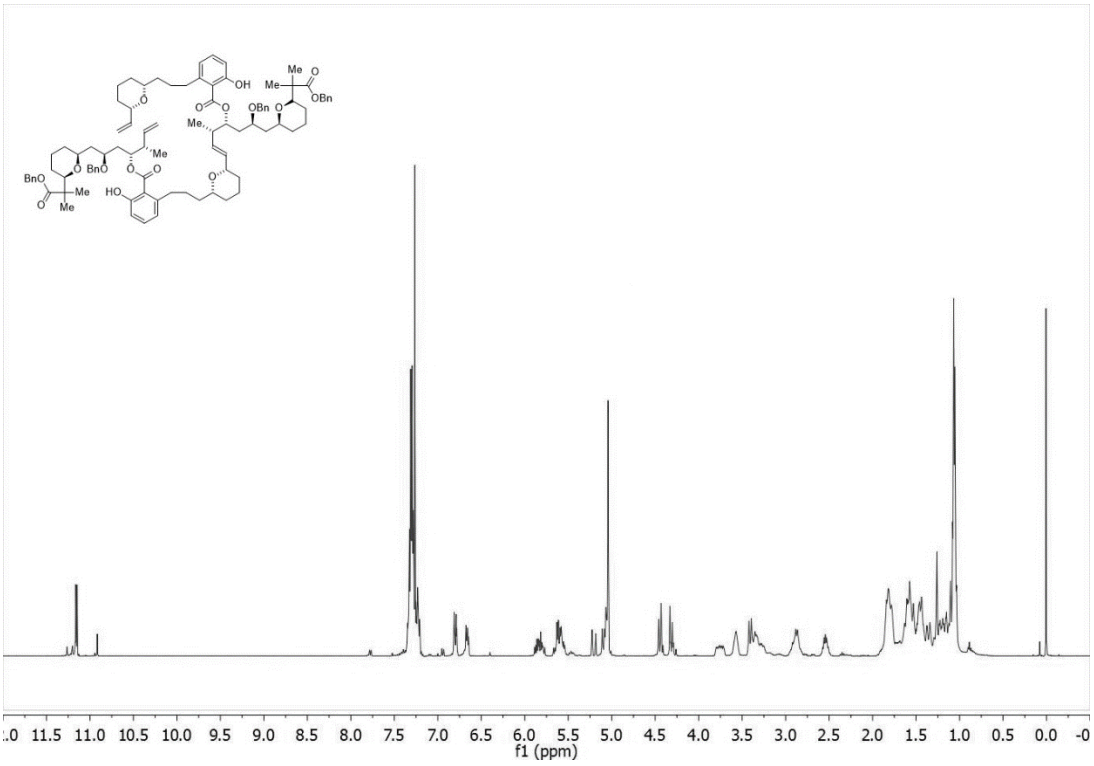
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), δ 11.14 (s, 1H), 7.36–7.19 (m, 22H), 6.82–6.77 (m, 2H), 6.69–6.63 (m, 2H), 5.90–5.75 (m, 2H), 5.67–5.52 (m, 4H), 5.24–5.00 (m, 8H), 4.48–4.40 (m, 2H), 4.34–4.25 (m, 2H), 3.82–3.69 (m, 2H), 3.61–3.53 (m, 2H), 3.44–3.21 (m, 6H), 2.97–2.79 (m, 4H), 2.60–2.48 (m, 2H), 1.89–1.73 (m, 11H), 1.66–1.32 (m, 21H), 1.30–1.00 (m, 26H).

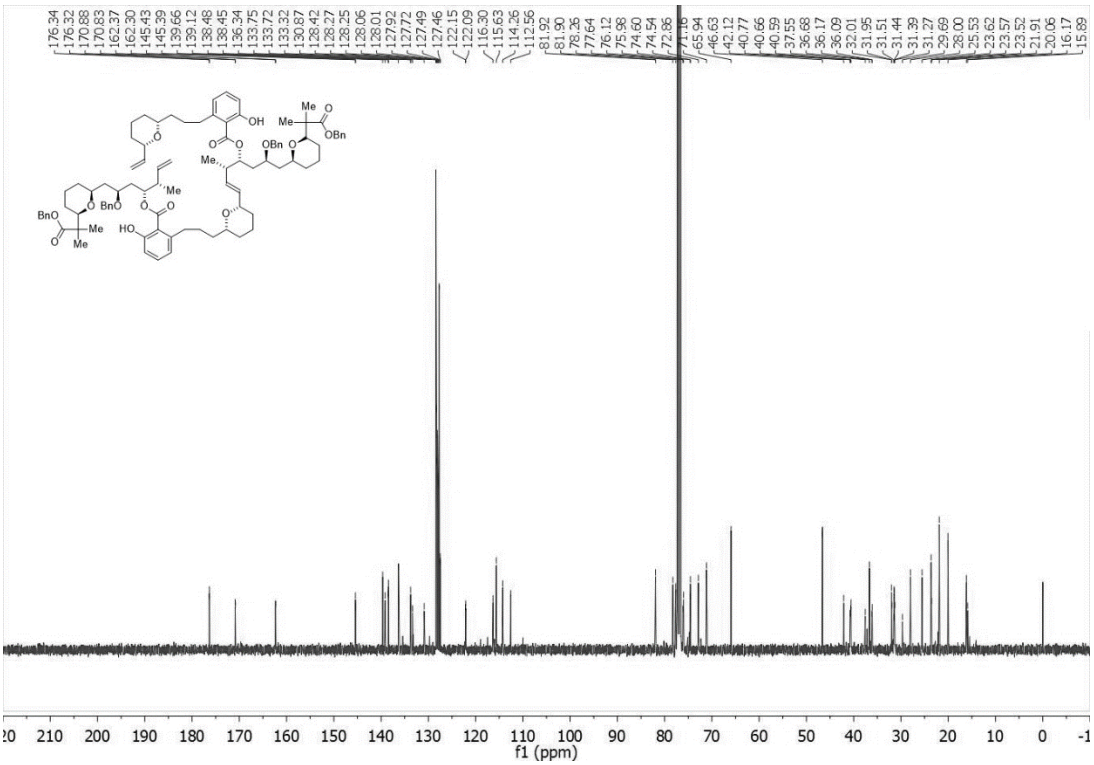
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 176.3, 170.9, 170.8, 162.4, 162.3, 145.4, 145.4, 139.7, 139.1, 138.5, 138.5, 136.3, 133.8, 133.7, 133.3, 130.9, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 127.5, 122.2, 122.1, 116.3, 115.6, 114.3, 112.6, 81.9, 81.9, 78.3, 77.6, 76.1, 76.0, 74.6, 74.5, 72.9, 71.2, 65.9, 46.6, 42.1, 40.8, 40.7, 40.6, 37.6, 36.7, 36.2, 36.1, 32.0, 32.0, 31.5, 31.4, 31.4, 31.3, 29.7, 28.0, 25.5, 23.6, 23.6, 23.5, 21.9, 20.1, 16.2, 15.9.

HRMS (ESI) Calcd. for $C_{94}H_{120}O_{16}Na$ $[M+Na]^+$: 1527.8469, Found: 1527.8443.

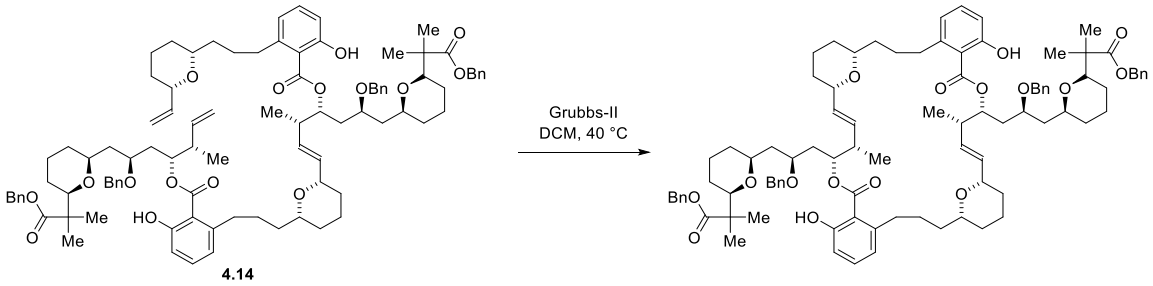
FTIR (neat): 2936, 2860, 1731, 1652, 1605, 1449, 1366, 1310, 1250, 1214, 1164, 1088, 1048, 918, 816, 738, 697 cm^{-1}.

$[\alpha]^{20}_D$ = +14.70° (c 1.0, $CHCl_3$).


f1 (ppm)


f1 (ppm)

(3*S*,4*R*,6*S*)-6-(benzyloxy)-7-((2*S*,6*S*)-6-(1-(benzyloxy)-2-methyl-1-oxopropan-2-yl)tetra-hydro-2*H*-pyran-2-yl)-3-methylhept-1-en-4-yl 2-hydroxy-6-(3-((2*S*,6*S*)-6-vinyltetra-hydro-2*H*-pyran-2-yl)propyl)benzoate dimer



Diene **4.14** (30.0 mg, 0.02 mmol, 100 mol%) and Grubbs' second generation catalyst (1.70 mg, 0.002 mmol, 10 mol%) were dissolved in dry DCM (6.70 mL, 0.003 M) and the solution was heated at 40 °C. After stirring for 10 h, the reaction was concentrated *in vacuo* and subjected to flash column chromatography (SiO_2: hexane/ethyl acetate, 20:1 to 6:1) to furnish the title product in 68% yield (20.1 mg, 0.0136 mmol).

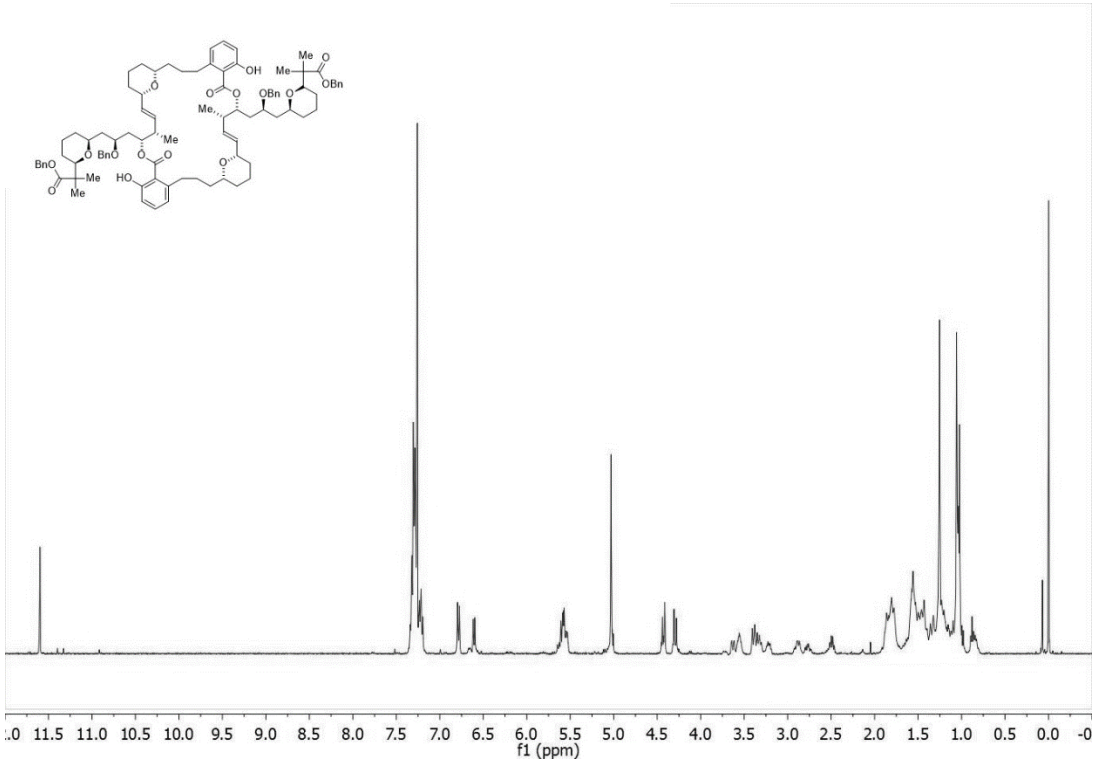
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (s, 2H), 7.35–7.18 (m, 22H), 6.79 (d, *J* = 8.3 Hz, 2H), 6.61 (d, *J* = 7.6 Hz, 2H), 5.66–5.52 (m, 6H), 5.03 (s, 4H), 4.43 (dd, *J* = 11.0, 4.9 Hz, 2H), 4.30 (dd, *J* = 11.4, 5.1 Hz, 2H), 3.63 (d, *J* = 11.2 Hz, 1H), 3.56 (s, 2H), 3.43–3.28 (m, 4H), 3.27–3.18 (m, 1H), 2.95–2.83 (m, 1H), 2.82–2.71 (m, 1H), 2.56–2.45 (m, 2H), 1.92–1.71 (m, 10H), 1.66–1.38 (m, 20H), 1.38–0.95 (m, 30H), 0.92–0.79 (m, 2H).

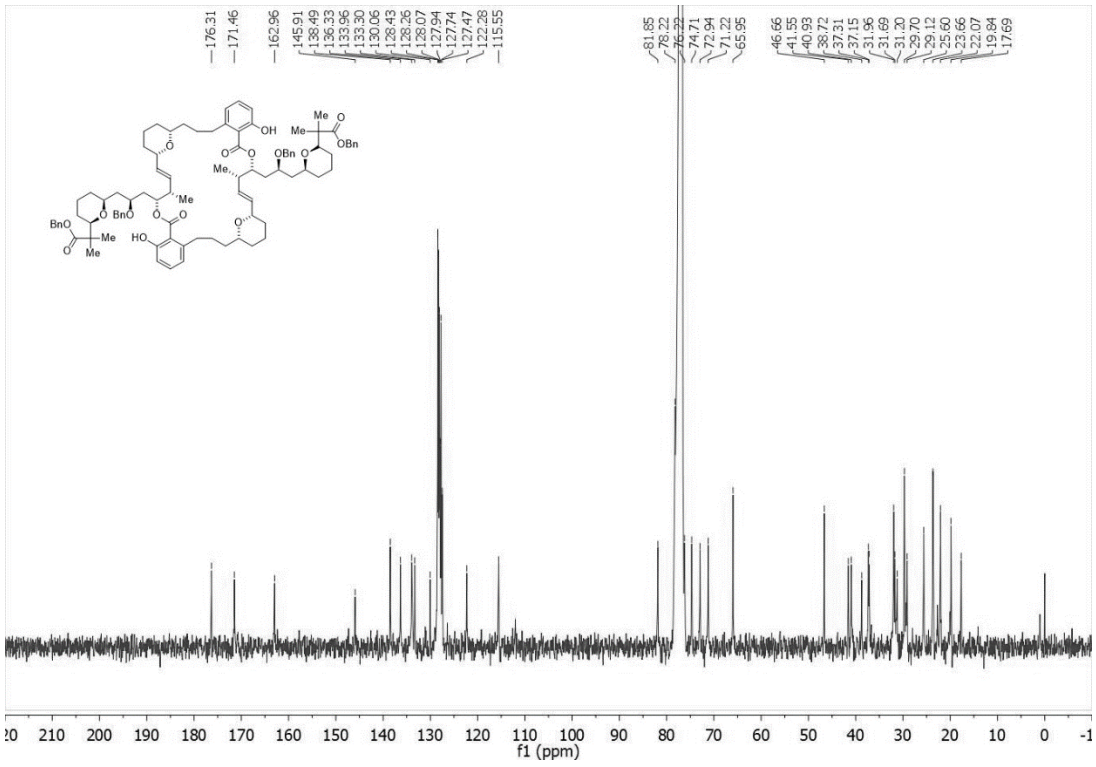
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 171.5, 163.0, 145.9, 138.5, 136.3, 134.0, 133.3, 130.1, 128.4, 128.3, 128.1, 127.9, 127.7, 127.5, 122.3, 115.6, 81.9, 78.2, 76.2, 74.7, 72.9, 71.2, 66.0, 46.7, 41.6, 40.9, 38.7, 37.3, 37.2, 32.0, 31.7, 31.2, 29.7, 29.1, 25.6, 23.7, 22.1, 19.8, 17.7.

HRMS (ESI) Calcd. for $C_{92}H_{116}O_{16}Na$ $[M+Na]^+$: 1499.8156, Found: 1499.8121.

FTIR (neat): 2918, 2603, 2359, 2205, 2158, 2106, 2091, 2052, 2037, 1733, 1714, 1698, 1651, 1574, 1537, 1454, 1253, 837 cm^{-1}.

$[\alpha]^{20}_D =$ +28.70° (c 0.5, $CHCl_3$).


f1 (ppm)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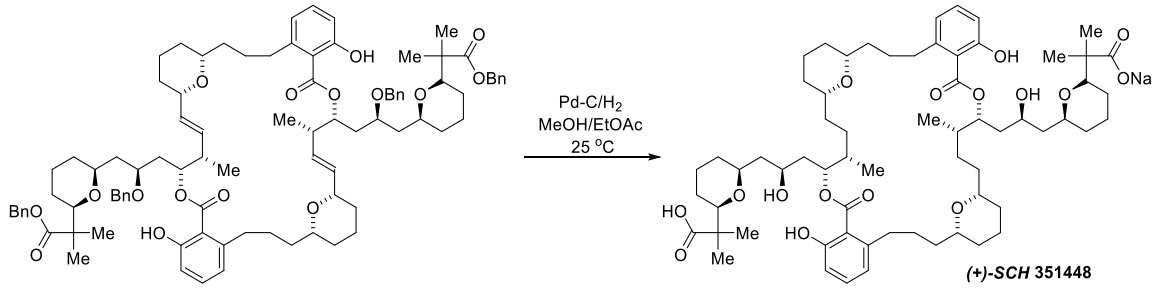
f1 (ppm)

(+)-**SCH 351448**



To a flask charged with diene (10.0 mg, 0.0067 mmol, 100 mol%) and Pd/C (10% w/w, 1.4 mg, 20 mol%), was added EtOAc (1 mL) and MeOH (3 mL). The reaction mixture was stirred under 1 atm H_2 (balloon) for 8 h. The solution was filtered and the filtrate was concentrated. The residue was diluted with 5 mL of hexane, and then washed with 2 mL of a 4 N HCl solution saturated with NaCl. The aqueous layer was extracted with 5 mL hexane. The combined organic solution was dried over Na_2SO_4 and concentrated *in vacuo* to afford crude (+)-SCH 351448 in 65% (5.0 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.9 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.72 (d, *J* = 7.5 Hz, 2H), 5.67–5.59 (m, 2H), 3.77–3.69 (m, 2H), 3.64–3.54 (m, 2H), 3.50 (d, *J* = 11.3 Hz, 2H), 3.19–3.06 (m, 6H), 2.60–2.48 (m, 2H), 2.10–2.00 (m, 2H), 1.90–1.80 (m, 4H), 1.80–1.72 (m, 2H), 1.73–1.62 (m, 6H), 1.63–1.55 (m, 4H), 1.56–1.37 (m, 22H), 1.36–1.18 (m, 10H), 1.12 (s, 6H), 1.09 (s, 6H), 1.01 (d, *J* = 6.7 Hz, 6H).

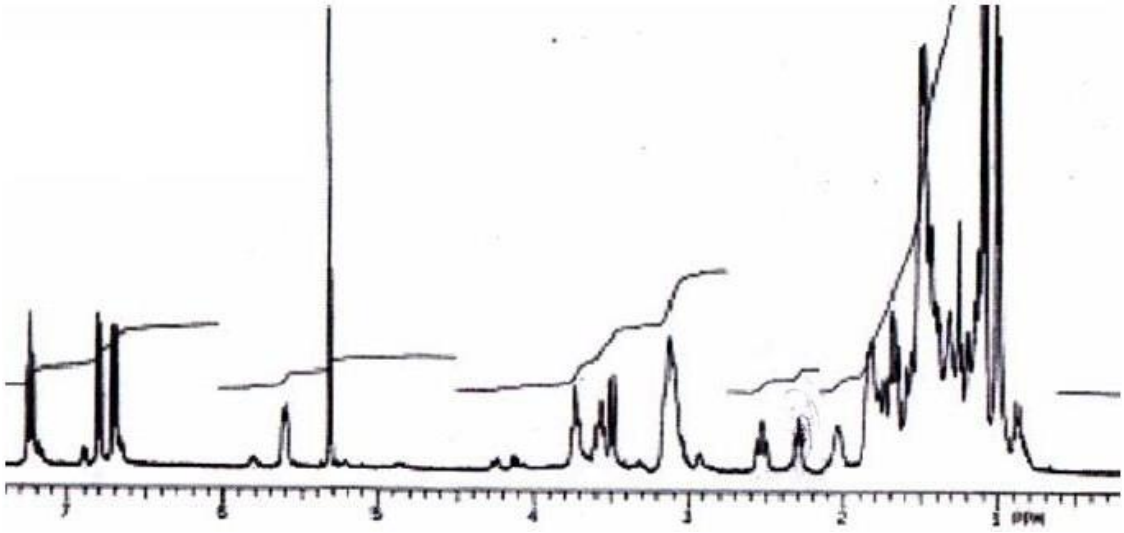
^{13}C NMR (151 MHz, CD_2Cl_2) δ 178.7, 171.1, 160.2, 145.1, 133.5, 122.4, 115.9, 115.5, 83.3, 79.2, 78.3, 78.1, 77.7, 67.5, 46.5, 43.7, 37.9, 37.5, 36.9, 36.6, 35.2, 32.9, 32.5, 32.0, 30.1, 29.5, 25.2, 24.3, 23.5, 23.2, 19.3, 15.1.

HRMS (ESI) Calcd. for $C_{64}H_{95}O_{16}Na$ $[M+Na]^+$: 1143.6591, Found: 1143.6574.

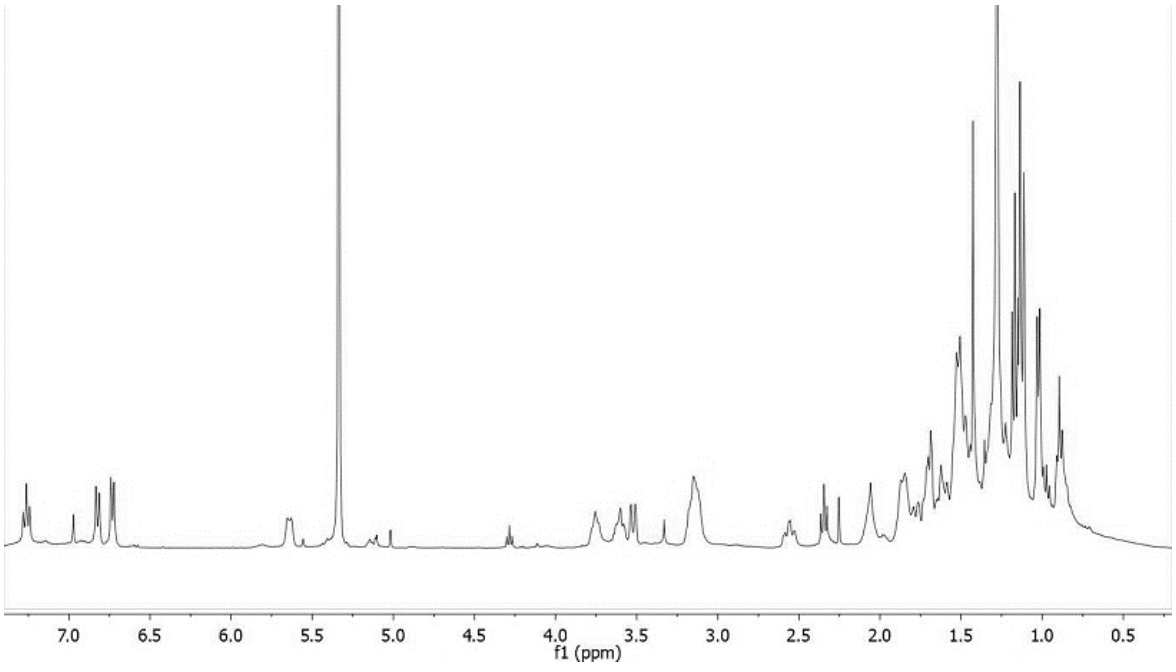
FTIR (neat): 3446, 2922, 2856, 1990, 1707, 1655, 1575, 1449, 1375, 1292, 1253, 1212, 1087, 1045 cm^{-1}.

$[\alpha]^{20}_D =$ +27.60° (c 0.3, $CHCl_3$).

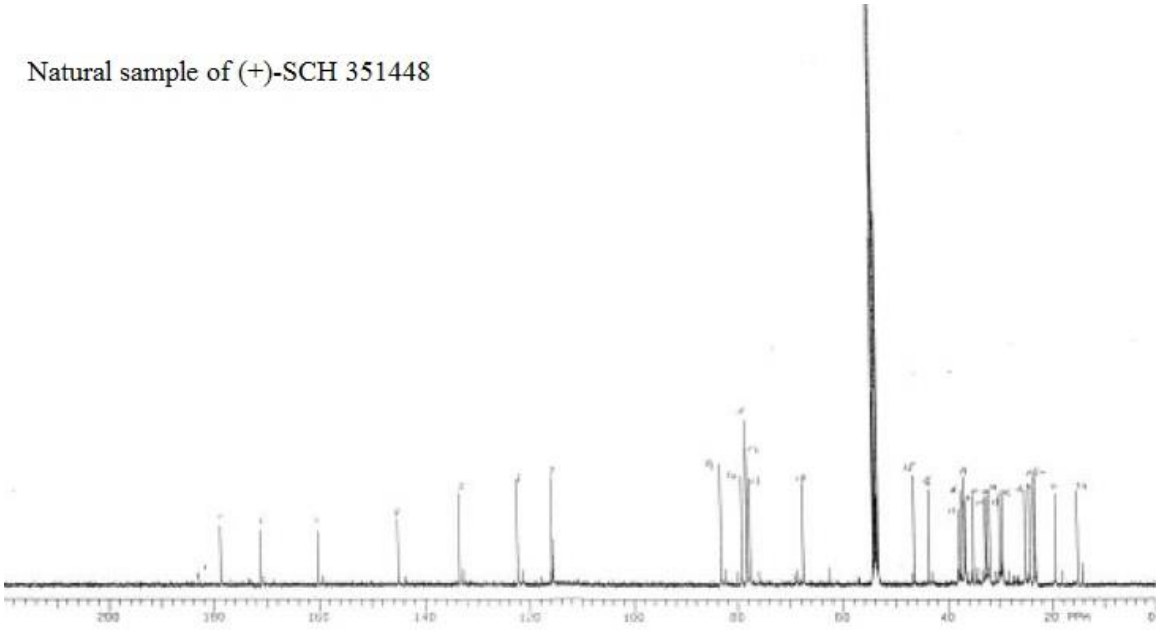
Natural sample of (+)-SCH 351448[34]



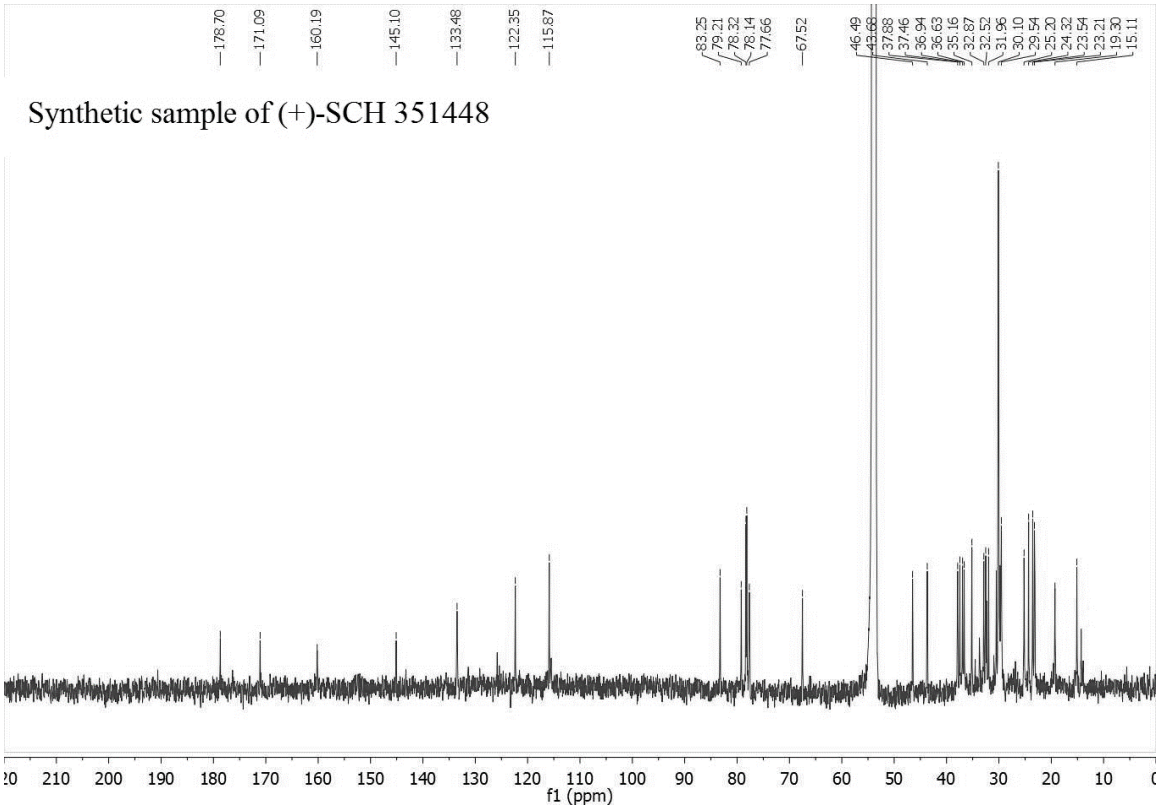
Synthetic sample of (+)-SCH 351448



Natural sample of (+)-SCH 351448



Synthetic sample of (+)-SCH 351448



^{13}C NMR comparison to the natural sample[35] of (+)-SCH 351448

Carbon #	**^{13}C (Hegde)**	**^{13}C (Krische)**
1	178.7	178.7
2	46.4	46.5
3	83.2	83.3
4	37.8	37.9
5	23.5	23.5
6	32.8	32.9
7	79.1	79.2
8	43.6	43.7
9	67.5	67.5
10	37.4	37.5
11	77.6	77.7
12	36.9	36.9
13	29.5	29.5
14	25.2	25.2
15	78.1	78.1
16	32.5	32.5
17	24.2	24.3
18	31.9	32.0
19	78.2	78.3
20	35.1	35.2
21	30.0	30.1
22	36.6	36.6
23	145.0	145.1
24	122.3	122.4
25	133.4	133.5
26	115.8	115.9
27	160.1	160.2
28	115.5	115.5
29	171.0	171.1
1-Me	19.3	19.3
1-Me	23.1	23.2
12-Me	15.0	15.1

Chapter 5: Regioselective Hydrohydroxyalkylation of Styrene with Primary Alcohols or Aldehydes via Ruthenium Catalyzed C-C Bond Forming Transfer Hydrogenation*

5.1 INTRODUCTION

The use of premetalated *C*-nucleophiles in carbonyl addition has opened immense volume of chemical space and is now a longstanding cornerstone of chemical synthesis since the work of Butlerov and Grignard.[1,2] As an alternative to classic carbonyl addition, the catalytic reductive coupling of π-unsaturated reactants with carbonyl compounds potentially avoids stoichiometric organometallic reagents and the issue of safety, selectivity and waste that attend their use (Figure 5.1).[3,5c] As exemplified by hydroformylation,[4] the prototypical catalytic reductive coupling, *byproduct-free* transformations are preferred for large volume chemical manufacture. Additionally, the identification of terminal reductants that are less costly than the coupling partners themselves is important. Hence, reductive couplings in which alcohols serve dually as hydrogen donors and carbonyl precursor are especially attractive.[5]

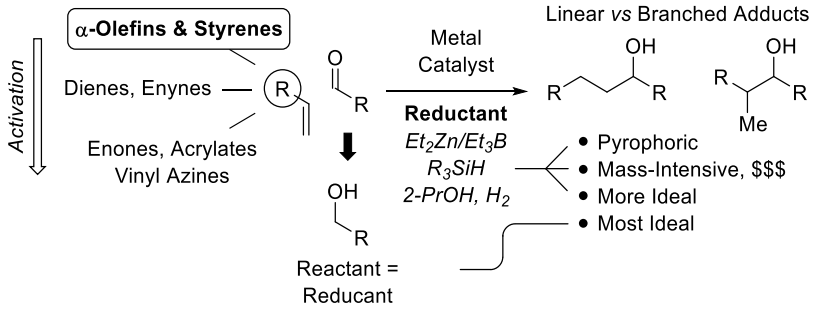
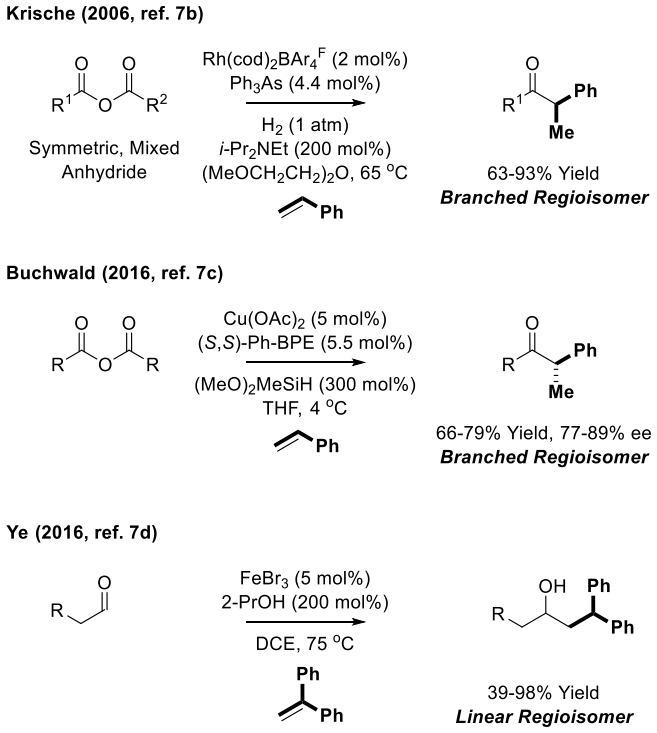


Figure 5.1 The catalytic reductive coupling of π-unsaturated reactants with carbonyl compounds.

* This chapter is based on the published work:
Xiao, H.; Wang, G.; Krische, M. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 16119.

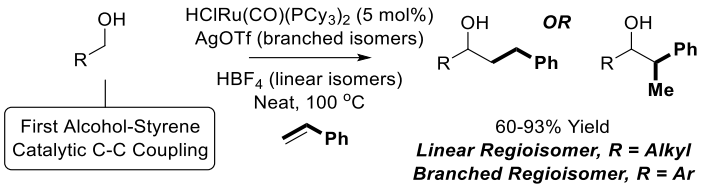
Styrene ranks among the most abundant π-unsaturated feedstocks (>25 x 10^6 tons/2010),[6] yet very few catalytic reductive coupling of styrene with carbonyl compounds have developed (Scheme 5.1). Following an initial report by Miura,[7a] the present author developed a rhodium catalyzed reductive coupling of styrene with carboxylic anhydrides mediated by elemental hydrogen.[7b] Recently, Buchwald reported an enantioselective copper-catalyzed variant of this transformation mediated by silane.[7c] These processes display branch-regioselectivity. In contrast, Ye reports a 2-propanol mediated reductive Prins reaction of vinyl arenes with aldehydes to form linear adducts.[7d] As anticipated based on the mechanism, this process is most efficient for olefins capable of stabilizing a cationic intermediate and only one example of styrene was described.



Scheme 5.1 Metal catalyzed reductive coupling of styrene with carbonyl compounds.

5.2 Reaction Development and Scope

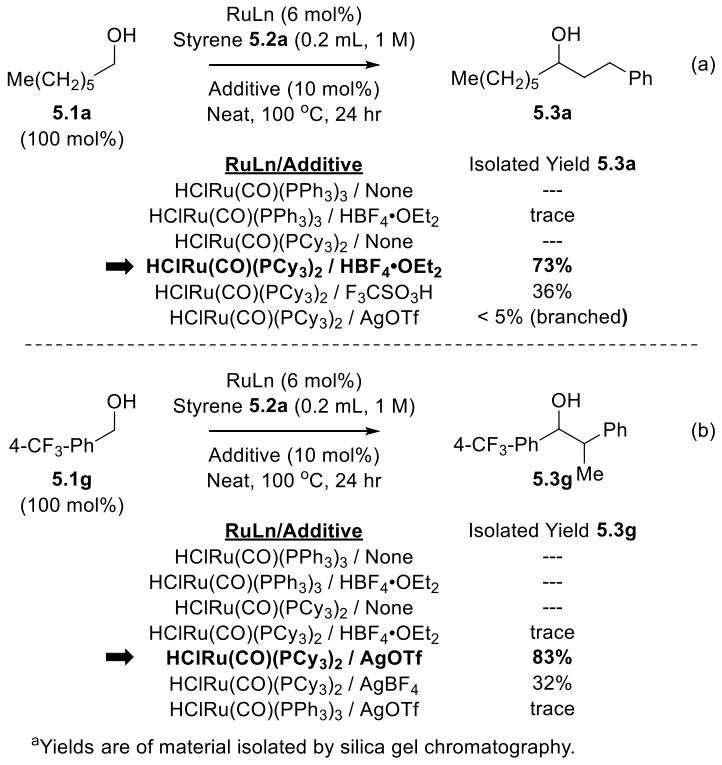
Here, we describe an intermolecular ruthenium catalyzed reductive coupling of unactivated aldehydes with styrene wherein primary alcohols serve dually as reductant and carbonyl precursor. Notably, using the precatalyst $HClRu(CO)(PCy_3)_2$ in combination with substoichiometric quantities of AgOTf or HBF_4, benzylic or aliphatic alcohols are converted to branched or linear adducts, respectively (Scheme 5.2).



Scheme 5.2 Ruthenium catalyzed reductive coupling of styrene with carbonyl compounds.

Our initial studies were inspired by Yi's observation that the addition of HBF_4•OEt_2 to the ruthenium-hydride complex $HClRu(CO)(PCy_3)_2$ dramatically enhances catalytic activity in alkene hydrogenation[8a] and hydrovinylation.[8b] As corroborated by mechanistic studies, HBF_4 serves to open a coordination site at ruthenium by protonating a tricyclohexylphosphine ligand.[8a] As demonstrated in our laboratory,[5,9,10] closely related ruthenium(II) carbonyl complexes catalyze the coupling of primary alcohols with diverse olefin pronucleophiles, including 1,3-dienes[9] and 1,3-enynes.[10] Despite longstanding effort, the use of styrene and α-olefins as pronucleophiles in C-C bond forming transfer hydrogenation remained an elusive challenge. Hence, a series of experiments were conducted to assess whether the use of HBF_4•OEt_2 might unlock reactions of this type (Scheme 5.3, a). Exposure of heptanol **5.1a** to styrene **5.2a** in the presence of commercially available $HClRu(CO)(PPh_3)_3$ did not lead to products of C-C coupling in the absence or presence of HBF_4•OEt_2. The related catalyst, $HClRu(CO)(PCy_3)_2$ was ineffective by itself,

however, in the presence of HBF_4•OEt_2 the linear product of C-C bond formation **5.3a** was formed in 73% yield as a single regioisomer. Other Brønsted acids were assayed, but were uniformly less effective.



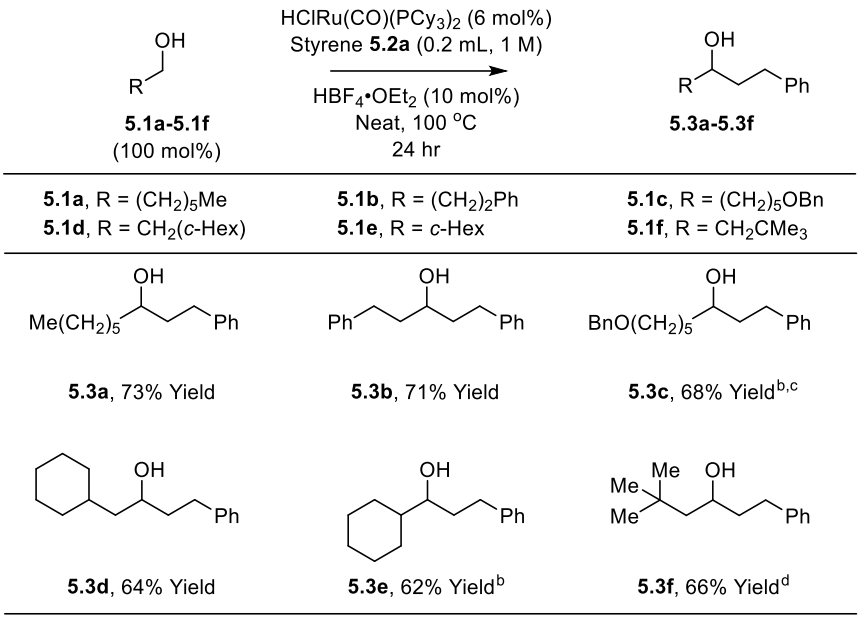
[a]Yields are of material isolated by silica gel chromatography.

Scheme 5.3 Selected optimization experiments for the ruthenium catalyzed C-C coupling of 1-heptanol **5.1a** and bicenzyl alcohol **5.1g** with styrene **5.2a**.[a]

Although the stoichiometric reaction of HBF_4•OEt_2 with $HClRu(CO)(PCy_3)_2$ was demonstrated by Yi to result in protonation of PCy_3,[5a] a control experiment was performed to rule out intervention of cationic ruthenium(II) complexes that potentially arise upon protonation of a hydride ligand.[9e,f] Specifically, the coupling of **5.1a** and **5.2a** was attempted using $HClRu(CO)(PCy_3)_2$ in the presence of AgOTf. Here, the linear regioisomer **5.3a** was not formed, yet a small quantity of the corresponding branched

regioisomer was detected. These data suggest cationic complexes do not catalyze reactions that form linear regioisomers and support the feasibility of optimizing a catalytic pathway to branched adducts. While aliphatic alcohols were recalcitrant partners for branch-selective coupling, the coupling of benzylic alcohol **5.1g** with styrene **5.2a** to form the branched adduct **5.3g** was amenable to optimization (Scheme 5.3, b).

Table 5.1 Ruthenium catalyzed C-C coupling of aliphatic alcohols **5.1a-5.1f** with styrene **5.2a** to form secondary alcohols **5.3a-5.3f**.[a]

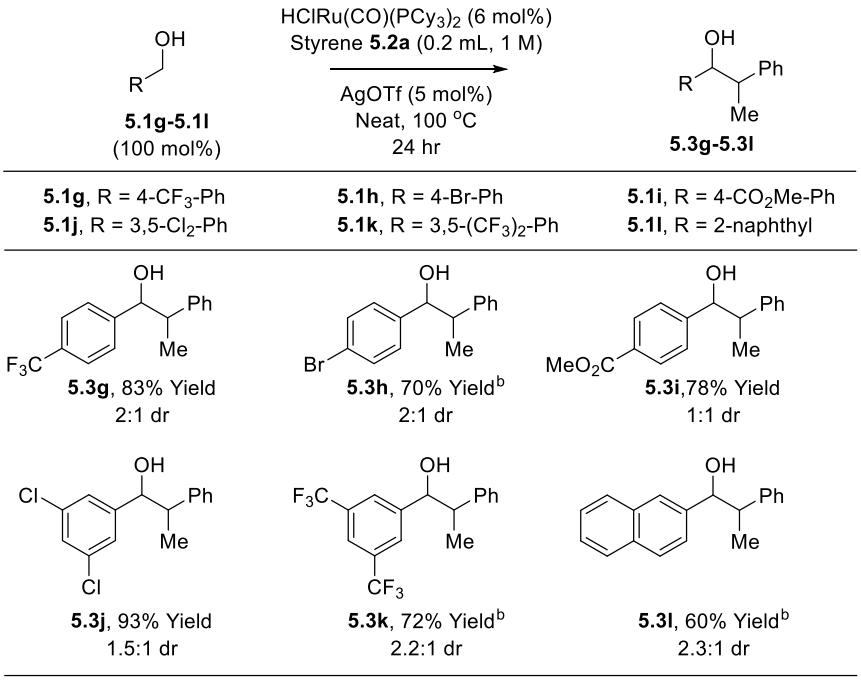


[a]Yields of material isolated by silica gel chromatography. See. [b]$HClRu(CO)(PCy_3)_2$ (10 mol%), HBF_4 (15 mol%). [c]styrene **5.2a** (0.4 mL), 120 °C. [d]2-PrOH (100 mol%).

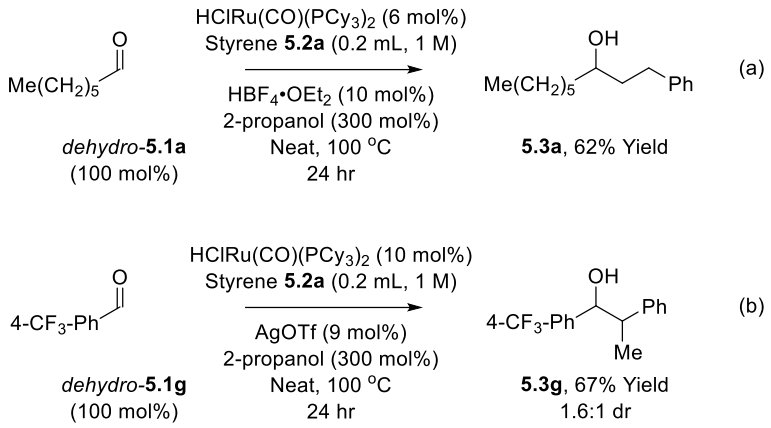
The scope of this regiodivergent transfer hydrogenative coupling of aliphatic and benzylic alcohols was briefly surveyed (Tables 5.1 and 5.2). The reaction of styrene **5.2a** with aliphatic alcohols **5.1a-5.1f** provided adducts **5.3a-5.3f** in good yield with complete levels of linear regioselectivity (Table 5.1). Even alcohols with branching at the β-position, such as cyclohexyl methanol **5.1e**, participate in C-C coupling although higher temperatures (120 °C) are required. The coupling of benzylic alcohols **5.1g-5.1l** delivered adducts **5.3g-5.3l** in good to excellent yields with complete branched regioselectivity

(Table 5.2). Here, electron deficient benzylic alcohols were more efficient partners for coupling. Beyond the redox-neutral couplings from the alcohol oxidation level, 2-propanol mediated reductive coupling of styrene **5.2a** with alkyl- and aryl-substituted aldehydes also is possible, as illustrated by the conversion of heptanal (*dehydro*-**5.1a**) to the linear secondary alcohol **3a** (Scheme 5.4, a) and the conversion of benzyl alcohol **5.1g** to the branched adduct **5.3g** (Scheme 5.4, b).

Table 5.2 Ruthenium catalyzed C-C coupling of benzylic alcohols **5.1g-5.1l** with styrene **5.2a** to form secondary alcohols **5.3g-5.3l**.[a]



[a]Yields of material isolated by silica gel chromatography. [b]HClRu(CO)(PCy$_3$)$_2$ (10 mol%), AgOTf (9 mol%).



Scheme 5.4 Ruthenium catalyzed C-C coupling of *dehydro*-**5.1a** and *dehydro*-**5.1g** with styrene **5.2a**.

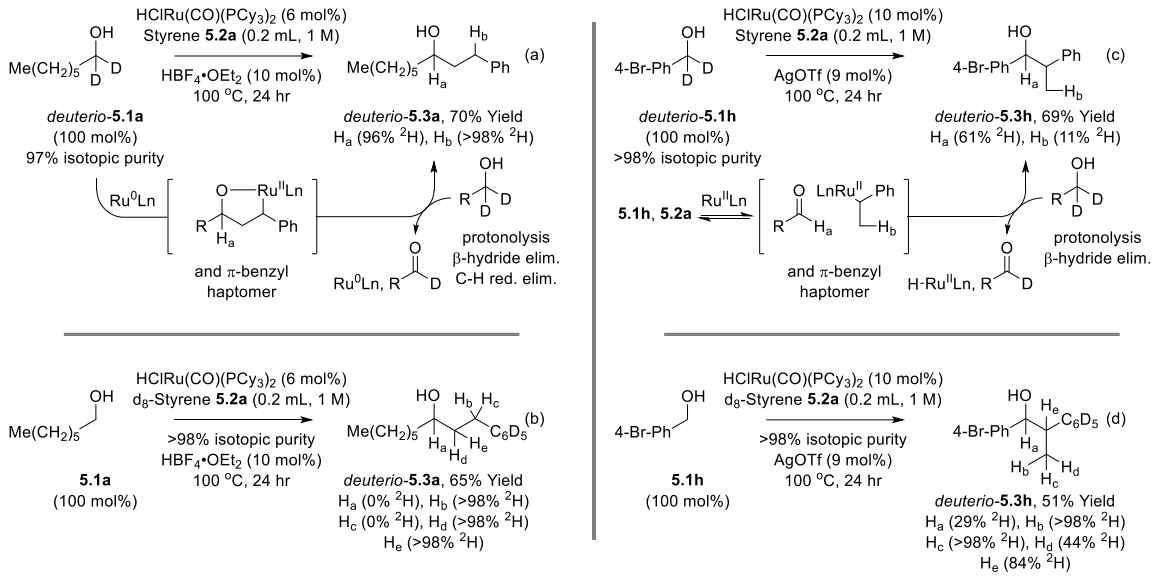
5.3 MECHANISM AND DISCUSSION

To gain insight into the catalytic mechanism, in particular the origins of linear vs. branched regioselectivity, a series of deuterium labelling experiments were performed (Scheme 5.5). Exposure of *deuterio*-**5.1a**, which is deuterated at the carbinol position (97% ^{2}H), to styrene **5.2a** under standard conditions results in the formation of *deuterio*-**5.3a** (Scheme 5.5, a). Complete retention of deuterium at the carbinol methane (96% ^{2}H) is accompanied by complete transfer of deuterium to the benzylic methylene (>98% ^{2}H). These data are consistent with a catalytic mechanism involving carbonyl-styrene oxidative coupling to form an oxaruthenacycle, which upon transfer hydrogenolysis mediated by *deuterio*-**5.1a** delivers *deuterio*-**5.3a**. Here, formation of a benzylic carbon-ruthenium bond defines the regioselectivity of oxaruthenacycle formation and, hence, the linear regioselectivity of C-C coupling. Although the primary alcohol reactant *deuterio*-**5.1a** dehydrogenates upon oxaruthenacycle transfer hydrogenolysis, the secondary alcohol product *deuterio*-**5.3a** appears kinetically unreactive toward dehydrogenation, presumably due to steric effects. A related deuterium labeling experiment in which alcohol **5.1a** is reacted with d_8-styrene **5.2a** provides a result consistent with this mechanistic

interpretation (Scheme 5.5, b). Exposure of *deuterio*-**5.1h**, to styrene **5.2a** under standard conditions for the coupling of benzylic alcohols provides *deuterio*-**5.3h** (Scheme 5.5, c). Significant loss of deuterium is observed at the carbinol methine (61% ^{2}H) and transfer of deuterium to the methyl hydrogen is incomplete (11% ^{2}H). Such loss of deuterium is consistent with a mechanism involving rapid, reversible hydrogen transfer between *deuterio*-**5.1h** and styrene **5.2a** to form aldehyde-benzylruthenium pairs in advance of turn-over limiting carbonyl addition. Here, hydrometalation to form a benzylic carbon-ruthenium bond defines the branched regioselectivity of C-C coupling. The related deuterium labeling experiment wherein the non-deuterated alcohol **5.1h** is reacted with d_8-styrene **5.2a** corroborates reversible transfer of hydrogen between alcohol **5.1h** and d_8-styrene **5.2a** (Scheme 5.5, d).

5.4 CONCLUSION

In summary, we report the first examples of metal catalyzed carbonyl-styrene C-C coupling. These processes can be conducted in redox-neutral manner from the alcohol oxidation level of the reactant via hydrogen auto-transfer. Alternatively, reductive coupling from the aldehyde oxidation level is possible using 2-propanol as an exogenous terminal reductant. Remarkably, the ruthenium precatalyst $HClRu(CO)(PCy_3)_2$ delivers branched or linear adducts from benzylic or aliphatic alcohols when modified by AgOTf or HBF_4, respectively.



[a]Yields are of material isolated by silica gel chromatography. Isotopic composition determined by HRMS, ^{1}H and ^{2}H NMR.

Scheme 5.5 General catalytic pathways accounting for linear *vs* branched regioselectivity as corroborated by deuterium labelling studies.[a]

5.5 EXPERIMENTAL DETAILS

General Information:

The ruthenium catalyst RuHCl(CO)(PCy_3)$_2$ was prepared according to the literature.[11] All reactions were run under an atmosphere of argon. Sealed tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator. Anhydrous solvents were transferred by oven-dried syringes. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F254). Visualization was accomplished with UV light followed by dipping in $KMnO_4$ stain solution then heating. Purification of reactions was carried out by flash chromatography using Silacycle silica gel (40-63 μm, unless indicated specifically). All silver salts were purchased from Alfa Aesar,

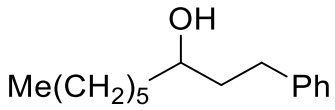
and stored in a desiccator. All alcohol substrates were purchased from commercially available sources and purified prior to use. Styrene was purchased from Sigma Aldrich and used without further purification. All aldehydes were used from commercially available sources, and purified via distillation in a Hickman still or column chromatography prior to use.

Spectroscopy, Spectrometry, and Data Collection:

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on an Agilent Technologies 6530 Accurate Mass Q-TOF LC/MS instrument and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M, M+H, or M-H), or a suitable fragment ion. ^{1}H nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Coupling constants are reported in Hertz (Hz) for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm). ^{13}C nuclear magnetic resonance spectra were recorded using a 100 MHz spectrometer for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CDCl_3$ δ_C (77.0 ppm). The products formed through C-C coupling from the alcohol and aldehyde oxidation levels are identical in all respects outside of diastereomeric ratios.

Detailed Procedures and Spectral Data for the Coupling Products 5.3a-5.3l:

1-phenylnonan-3-ol (5.3a)



From alcohol oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with 1-heptanol (23.2 mg, 0.2 mmol, 100 mol%) and $RuHCl(CO)(PCy_3)_2$ (8.7 mg, 0.012 mmol, 6 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe followed by $HBF_4{\cdot}Et_2O$ (5.5 μL, 0.02 mmol, 10 mol%). The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 40:1) to furnish the title compound (32.2 mg, 0.146 mmol) as a colorless oil in 73% yield.

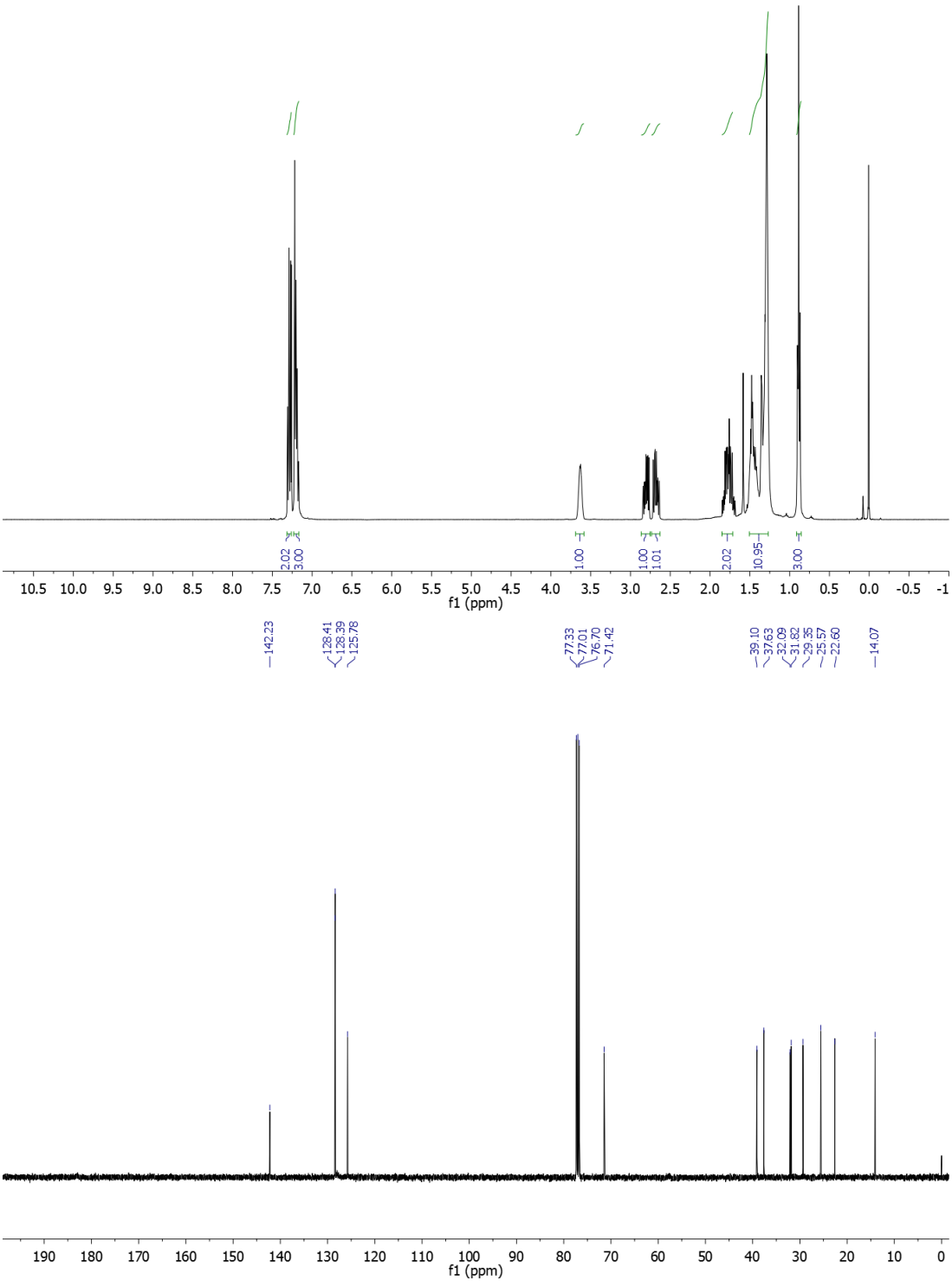
From aldehyde oxidation level: An oven-dried pressure tube equipped with a magnetic stir bar was charged with heptanal (22.8 mg, 0.2 mmol, 100 mol%) and $RuHCl(CO)(PCy_3)_2$ (8.7 mg, 0.012 mmol, 6 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) and 2-propanol (36 mg, 0.6 mmol, 300 mol%) were added by syringe followed by $HBF_4{\cdot}Et_2O$ (5.5 μL, 0.02 mmol, 10 mol%). The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 40:1) to furnish the title compound (27.3 mg, 0.124 mmol) as a colorless oil in 62% yield.

^{1}H NMR: (400 MHz, $CDCl_3$) δ7.32–7.26 (m, 2H), 7.24–7.16 (m, 3H), 3.63 (dq, *J* = 8.2, 3.9 Hz, 1H), 2.80 (ddd, *J* = 13.9, 9.7, 5.8 Hz, 1H), 2.68 (ddd, *J* = 13.8, 9.6, 6.6 Hz, 1H), 1.87–1.67 (m, 2H), 1.55–1.24 (m, 11H), 0.96–0.83 (m, 3H).

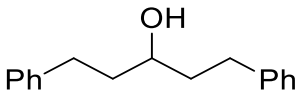
^{13}C NMR: (100 MHz, $CDCl_3$) δ 142.2, 128.4, 128.4, 125.8, 71.4, 39.1, 37.6, 32.1, 31.8, 29.4, 25.6, 22.6, 14.1.

HRMS: (CI) Calcd. For $C_{15}H_{23}O$ $[M-H]^-$ 219.1749, Found 219.1750.

FTIR: (neat): 3345, 2927, 2855, 1494, 1453, 1029, 746, 698 cm^{-1}.


2.02
3.00
1.00
1.00
1.01
2.02
10.95
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)
142.23
128.41
128.39
125.78
77.33
77.01
76.70
71.42
39.10
37.63
32.09
31.82
29.35
25.57
22.60
14.07
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

1,5-diphenylpentan-3-ol (5.3b)



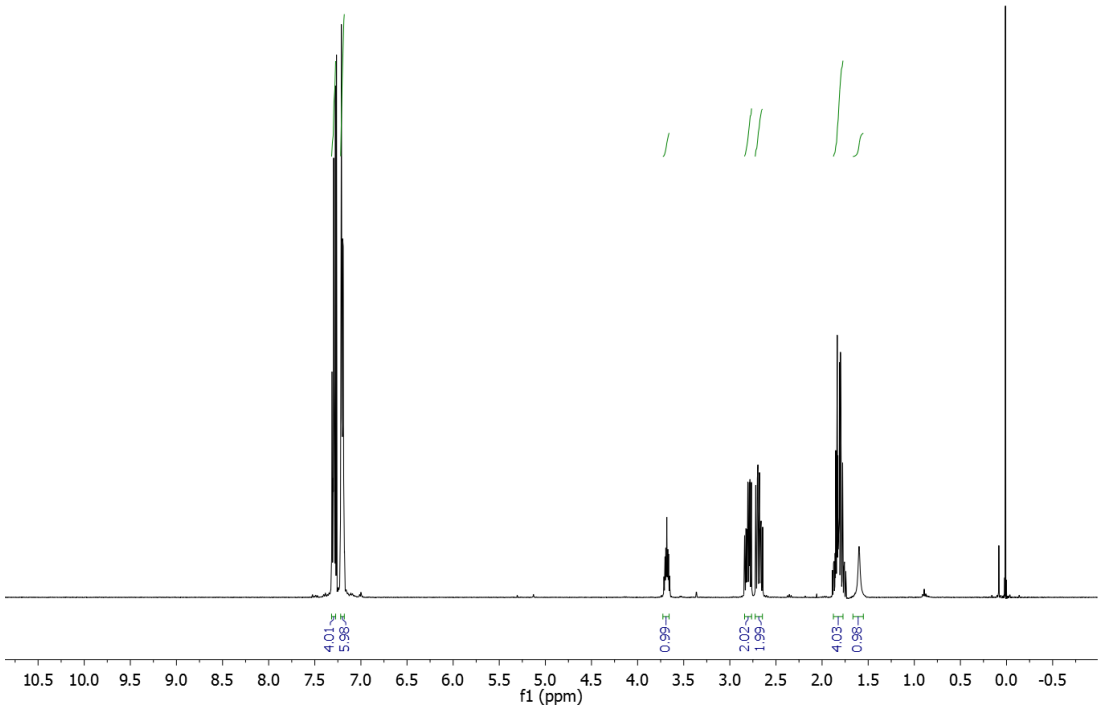
An oven-dried pressure tube equipped with a magnetic stir bar was charged with 3-phenylpropan-1-ol (27.2 mg, 0.2 mmol, 100 mol%) and $RuHCl(CO)(PCy_3)_2$ (8.7 mg, 0.012 mmol, 6 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe followed by $HBF_4{\cdot}Et_2O$ (5.5 μL, 0.02 mmol, 10 mol%). The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 20:1) to furnish the title compound (34.1 mg, 0.142 mmol) as a colorless oil in 71% yield.

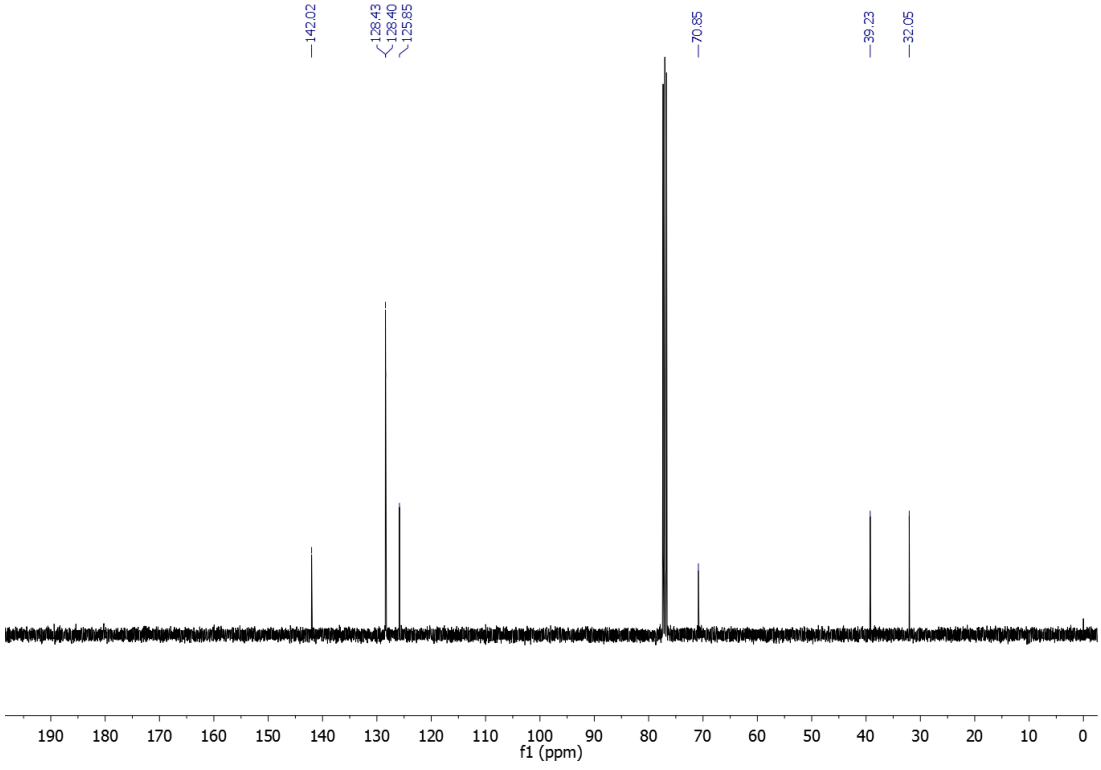
^{1}H NMR: (400 MHz, $CDCl_3$) δ7.32–7.27 (m, 4H), 7.23–7.18 (m, 6H), 3.68 (tt, J = 7.8, 4.5 Hz, 1H), 2.80 (ddd, J = 13.6, 9.5, 6.1 Hz, 2H), 2.68 (ddd, J = 13.7, 9.5, 6.8 Hz, 2H), 1.90–1.72 (m, 4H), 1.60 (s, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 142.0, 128.4, 128.4, 125.9, 70.9, 39.2, 32.1.

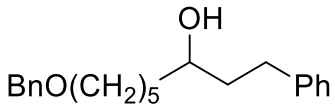
HRMS: (CI) Calcd. For $C_{17}H_{21}O$ $[M+H]^+$ 241.1592, Found 241.1591.

FTIR: (neat): 3382, 3025, 2930, 2856, 1602, 1495, 1453, 1261, 1091, 1030, 800, 747, 698 cm^{-1}.


4.01
5.98
0.99
2.02
1.99
4.03
0.98
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


142.02
128.43
128.40
125.85
70.85
39.23
32.05
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

8-(benzyloxy)-1-phenyloctan-3-ol (5.3c)



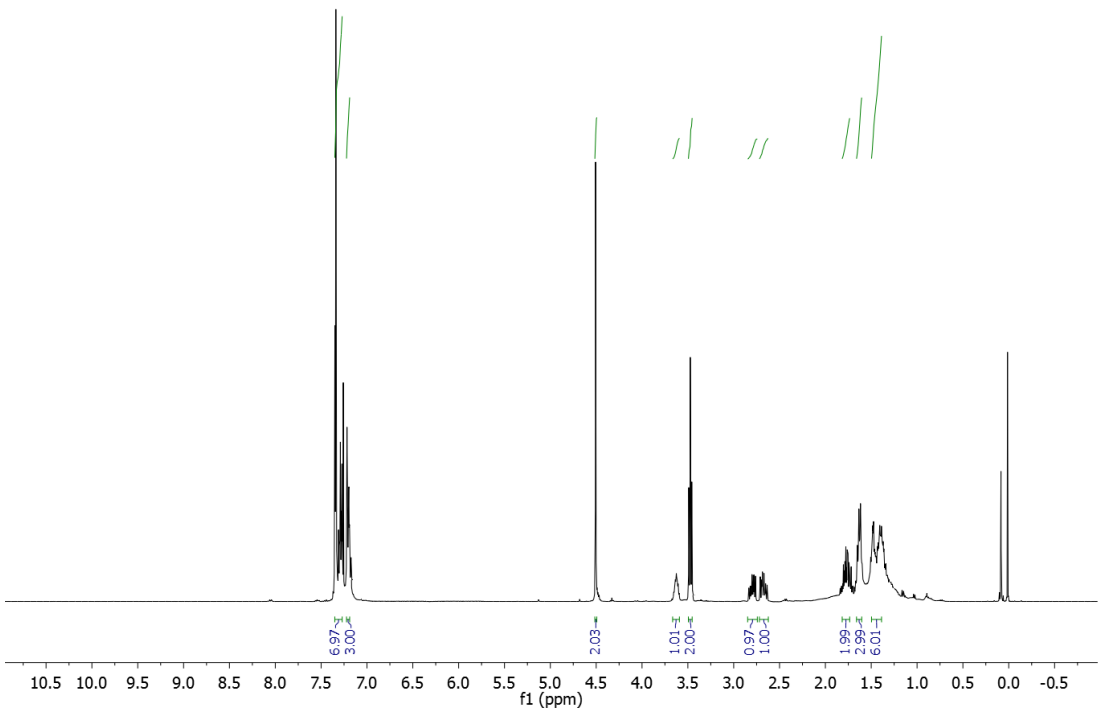
An oven-dried pressure tube equipped with a magnetic stir bar was charged with 6-(benzyloxy)hexan-1-ol (41.7 mg, 0.2 mmol, 100 mol%) and $RuHCl(CO)(PCy_3)_2$ (14.5 mg, 0.02 mmol, 10 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.4 mL, 0.5 M) was added by syringe followed by $HBF_4{\cdot}Et_2O$ (8.3 µL, 0.03 mmol, 15 mol%). The reaction vessel was sealed and the reaction mixture was allowed to stir at 120 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 20:1) to furnish the title compound (42.5 mg, 0.136 mmol) as a colorless oil in 68% yield

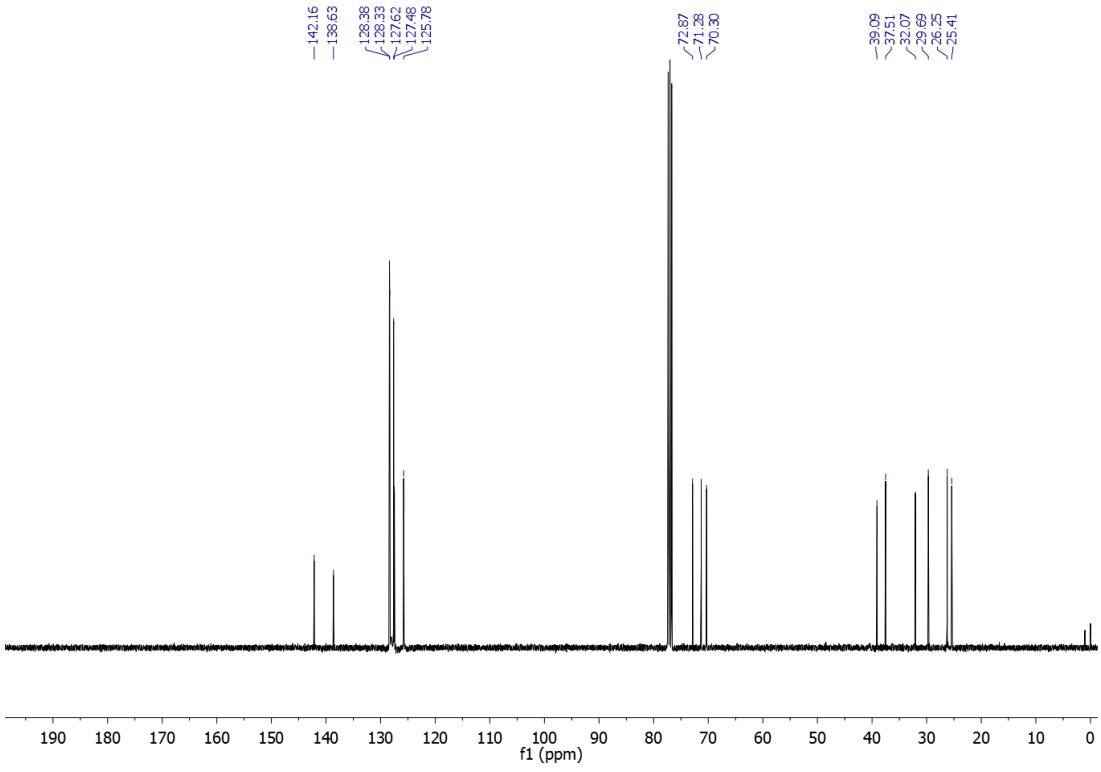
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 7H), 7.21 (dt, *J* = 8.1, 2.0 Hz, 3H), 4.51 (s, 2H), 3.63 (tt, *J* = 8.5, 4.2 Hz, 1H), 3.47 (t, *J* = 6.6 Hz, 2H), 2.80 (ddd, *J* = 13.8, 9.6, 5.9 Hz, 1H), 2.67 (ddd, *J* = 13.7, 9.6, 6.7 Hz, 1H), 1.81–1.73 (m, 2H), 1.63 (dd, *J* = 8.7, 5.0 Hz, 3H), 1.50–1.38 (m, 6H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ 142.2, 138.6, 128.4, 128.3, 127.6, 127.5, 125.8, 72.9, 71.3, 70.3, 39.1, 37.5, 32.1, 29.7, 26.3, 25.4.

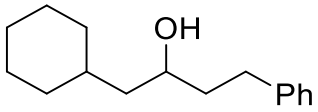
HRMS: (CI) Calcd. For $C_{21}H_{29}O_2$ $[M+H]^+$ 313.2168, Found 313.2174.

FTIR: (neat): 3406, 3060, 3025, 2929, 2855, 1567, 1493, 1452, 1364, 1098, 1028, 857, 797, 745, 698 cm^{-1}.


6.97
3.00
2.03
1.01
2.00
0.97
1.00
1.99
2.99
6.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


142.16
138.63
128.38
128.33
127.62
127.48
125.78
72.87
71.28
70.30
39.09
37.51
32.07
29.69
26.25
25.41
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

1-cyclohexyl-4-phenylbutan-2-ol (5.3d)



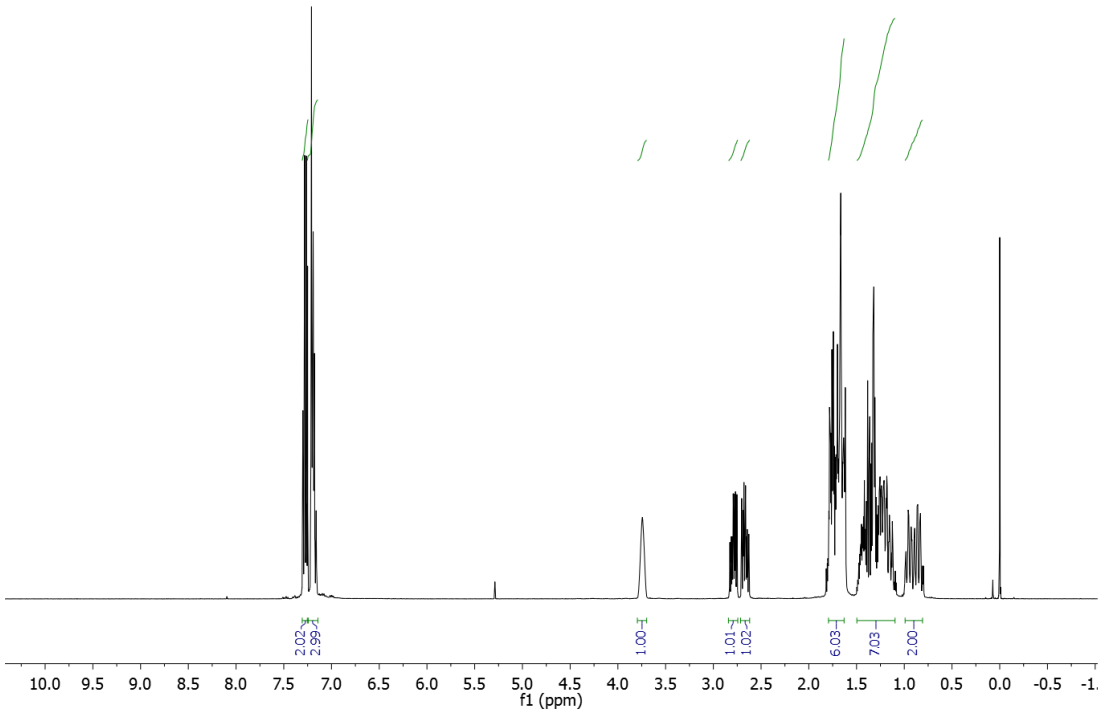
An oven-dried pressure tube equipped with a magnetic stir bar was charged with 2-cyclohexylethan-1-ol (25.6 mg, 0.2 mmol, 100 mol%) and $RuHCl(CO)(PCy_3)_2$ (8.7 mg, 0.012 mmol, 6 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe followed by $HBF_4{\cdot}Et_2O$ (5.5 μL, 0.02 mmol, 10 mol%). The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 40:1) to furnish the title compound (29.8 mg, 0.128 mmol) as a colorless oil in 64% yield.

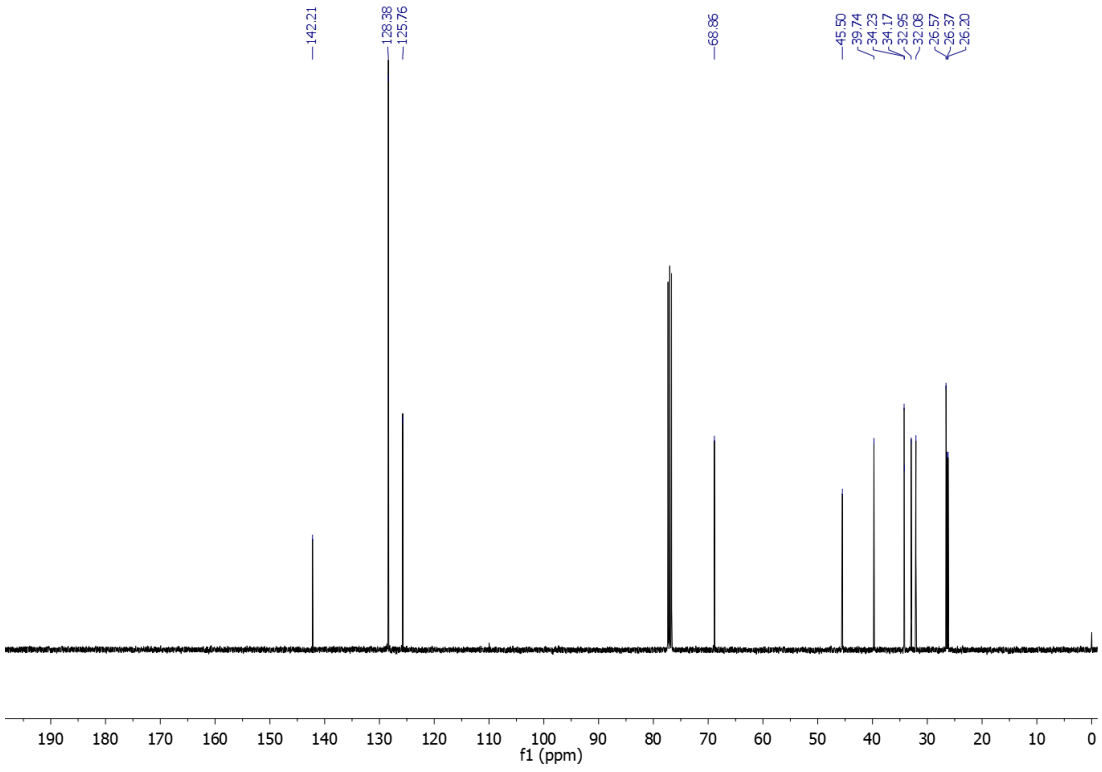
^{1}H NMR: (400 MHz, Chloroform-*d*) δ 3.74 (t, *J* = 6.5 Hz, 1H), 2.79 (ddd, *J* = 13.7, 9.7, 6.0 Hz, 1H), 2.67 (ddd, *J* = 13.8, 9.7, 6.6 Hz, 1H), 1.81–1.63 (m, 5H), 1.50–1.09 (m, 6H), 1.01–0.77 (m, 2H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 142.2, 128.4, 125.8, 68.9, 45.5, 39.7, 34.2, 34.2, 33.0, 32.1, 26.6, 26.4, 26.2.

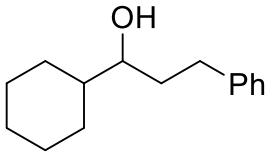
HRMS: (CI) Calcd. For $C_{16}H_{23}O$ $[M-H]^+$ 231.1749, Found 231.1746.

FTIR: (neat): 3336, 2919, 2850, 1494, 1448, 1068, 1046, 1000, 931, 745, 697 cm^{-1}.


2.02
2.99
1.00
1.01
1.02
6.03
7.03
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


142.21
128.38
125.76
68.86
45.50
39.74
34.23
34.17
32.95
32.08
26.57
26.37
26.20
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

1-cyclohexyl-3-phenylpropan-1-ol (5.3e)



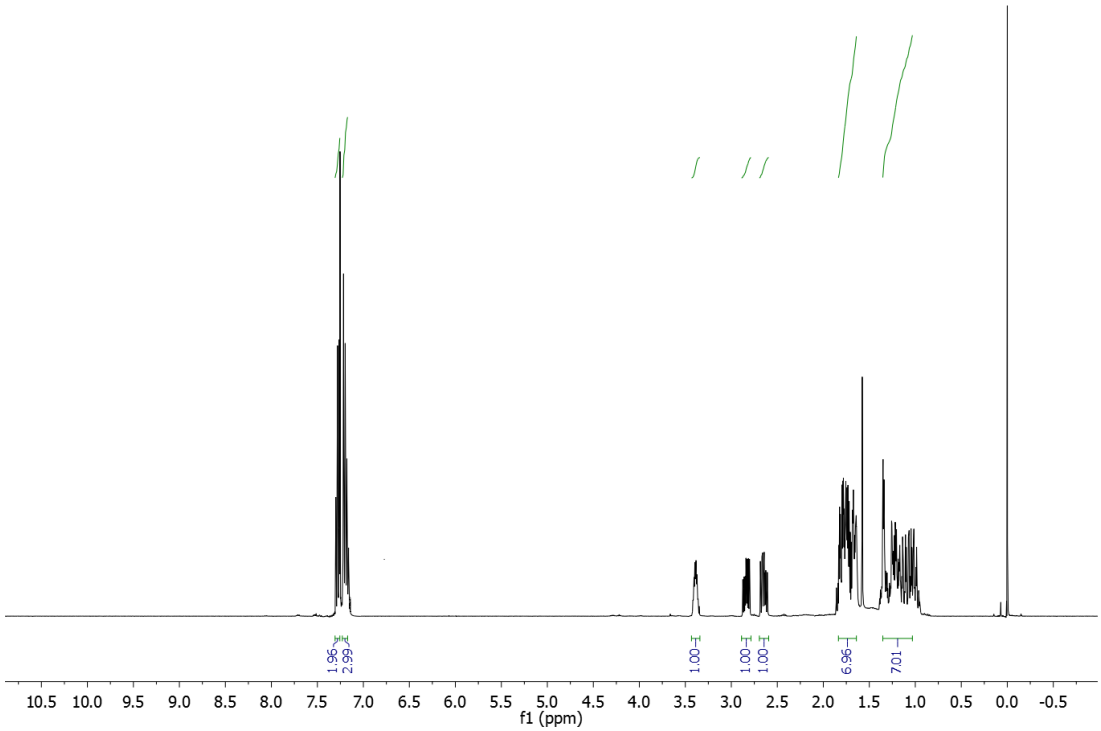
An oven-dried pressure tube equipped with a magnetic stir bar was charged with cyclohexylmethanol (22.8 mg, 0.2 mmol, 100 mol%) and $RuHCl(CO)(PCy_3)_2$ (14.5 mg, 0.02 mmol, 10 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe followed by $HBF_4{\cdot}Et_2O$ (8.3 μL, 0.03 mmol, 15 mol%). The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 40:1) to furnish the title compound (27.1 mg, 0.124 mmol) as a colorless oil in 62% yield.

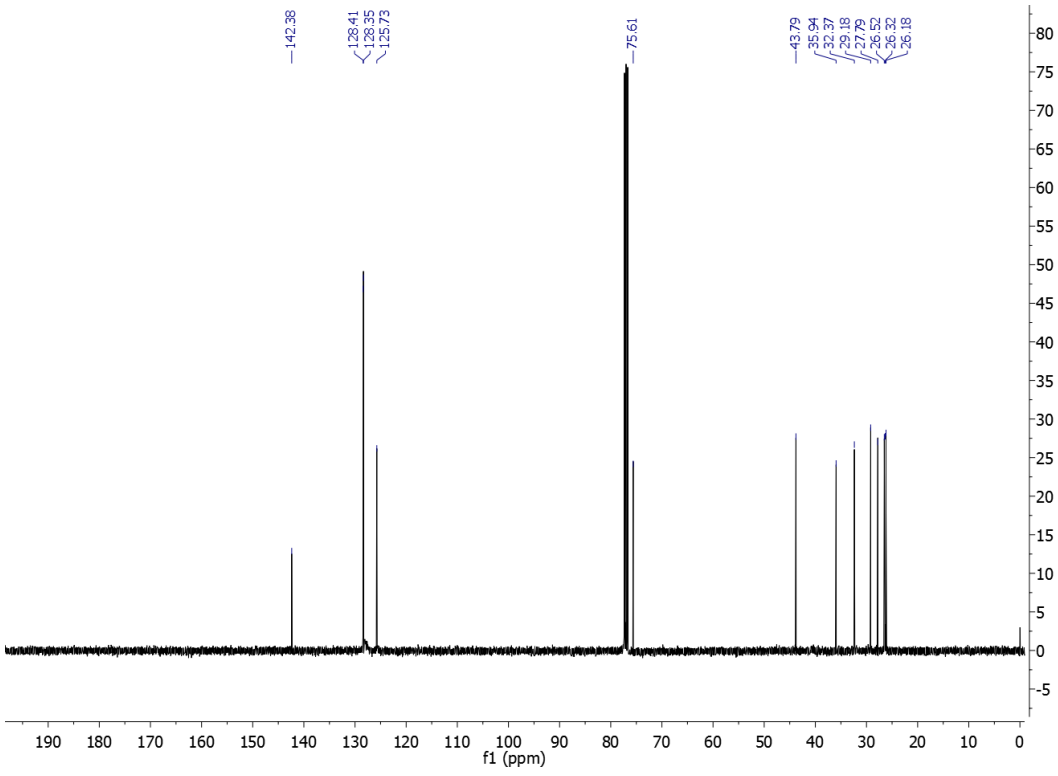
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.24–7.16 (m, 3H), 3.44–3.36 (m, 1H), 2.85 (ddd, *J* = 13.7, 10.1, 5.3 Hz, 1H), 2.66 (ddd, *J* = 13.7, 9.8, 6.6 Hz, 1H), 1.92–1.62 (m, 7H), 1.39–0.98 (m, 7H).

^{13}C NMR: (100 MHz, CDCl3) δ 142.4, 128.4, 128.4, 125.7, 75.6, 43.8, 35.9, 32.4, 29.2, 27.8, 26.5, 26.3, 26.2.

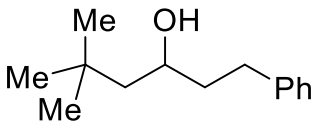
HRMS: (CI) Calcd. For $C_{15}H_{21}O$ $[M-H]^-$ 217.1592, Found 217.1601.

FTIR: (neat): 3365, 3026, 2923, 2851, 1602, 1494, 1451, 1064, 1030, 748, 698 cm^{-1}.


1.96
2.99
1.00
1.00
1.00
6.96
7.01
f1 (ppm)


142.38
128.41
128.35
125.73
75.61
43.79
35.94
32.37
29.18
27.79
26.52
26.32
26.18
f1 (ppm)

5,5-dimethyl-1-phenylhexan-3-ol (5.3f)



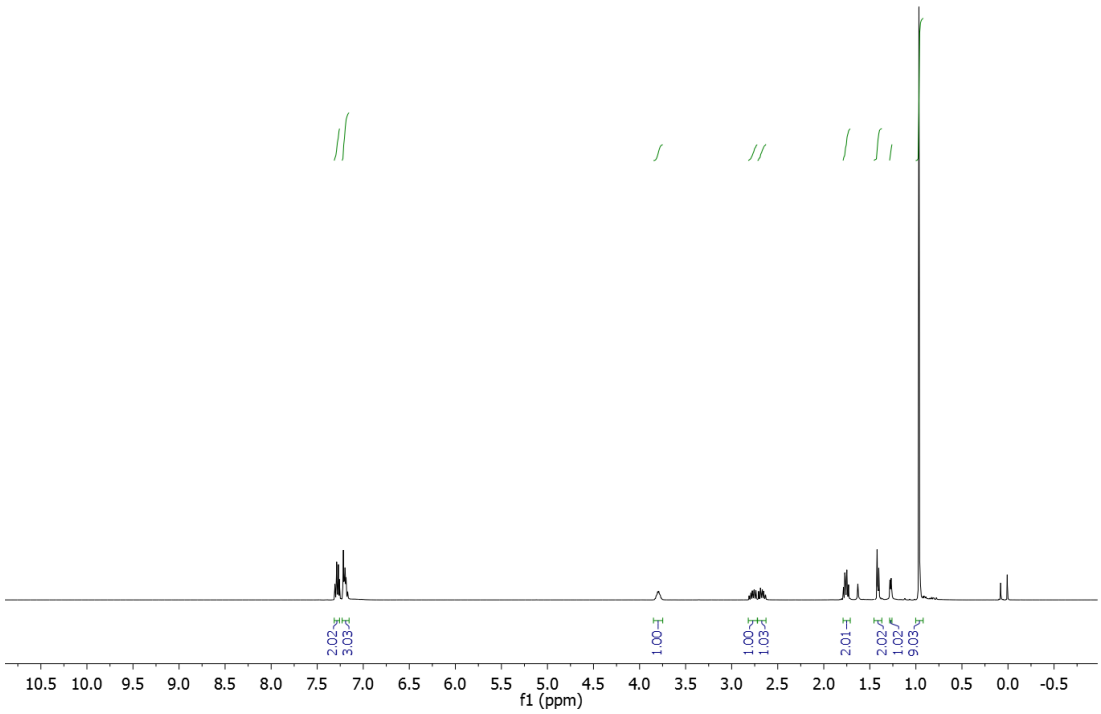
An oven-dried pressure tube equipped with a magnetic stir bar was charged with 3,3-dimethylbutan-1-ol (20.4 mg, 0.2 mmol, 100 mol%) and $RuHCl(CO)(PCy_3)_2$ (8.7 mg, 0.012 mmol, 6 mol%). The reaction vessel was placed under an atmosphere of argon, isopropyl alcohol (12 mg, 15μL, 0.2 mmol, 100 mol%) was added by syringe. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe followed by $HBF_4{\cdot}Et_2O$ (5.5 μL, 0.02 mmol, 10 mol%). The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 40:1) to furnish the title compound (27.2 mg, 0.132 mmol) as a colorless oil in 66% yield.

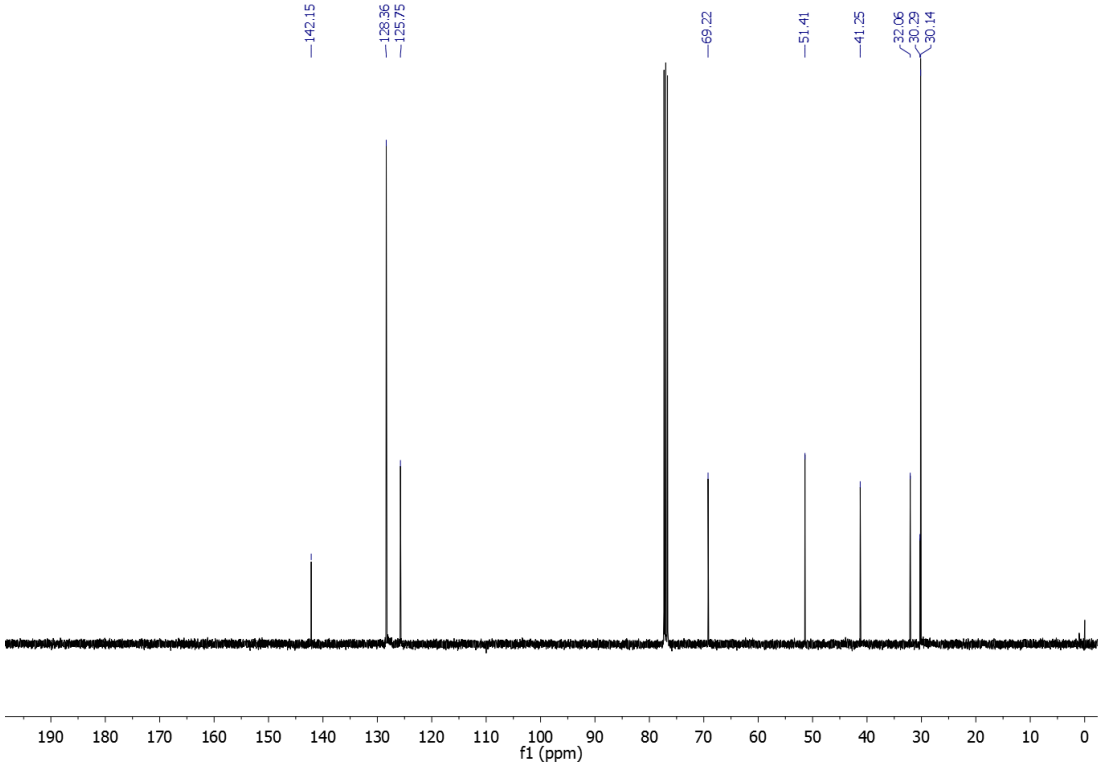
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 2H), 7.24–7.16 (m, 3H), 3.80 (h, J = 5.8 Hz, 1H), 2.82–2.73 (m, 1H), 2.72–2.63 (m, 1H), 1.80–1.72 (m, 2H), 1.45–1.38 (m, 2H), 0.97 (d, J = 0.9 Hz, 9H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ 142.2, 128.4, 125.8, 69.2, 51.4, 41.3, 32.1, 30.3, 30.1.

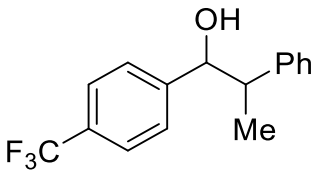
HRMS: (CI) Calcd. For $C_{14}H_{22}O$ $[M-H]^-$ 206.1671, Found 206.1679.

FTIR: (neat): 3394, 3026, 2950, 2865, 1495, 1474, 1454, 1364, 1249, 1060, 1029, 743, 698 cm^{-1}.


2.02
3.03
1.00
1.00
1.03
2.01
2.02
1.02
9.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


142.15
128.36
125.75
69.22
51.41
41.25
32.06
30.29
30.14
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

2-phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (5.3g)



<u>*From alcohol oxidation level:*</u> An oven-dried pressure tube equipped with a magnetic stir bar was charged with 4-(trifluoromethyl)benzyl alcohol (35.2 mg, 0.2 mmol, 100 mol%), $RuHCl(CO)(PCy_3)_2$ (8.7 mg, 0.012 mmol, 6 mol%), and AgOTf (2.6 mg, 0.01 mmol, 5 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 30:1) to furnish the title compound (46.5 mg, 0.166 mmol, *dr*: 2:1) as a colorless oil in 83% yield.

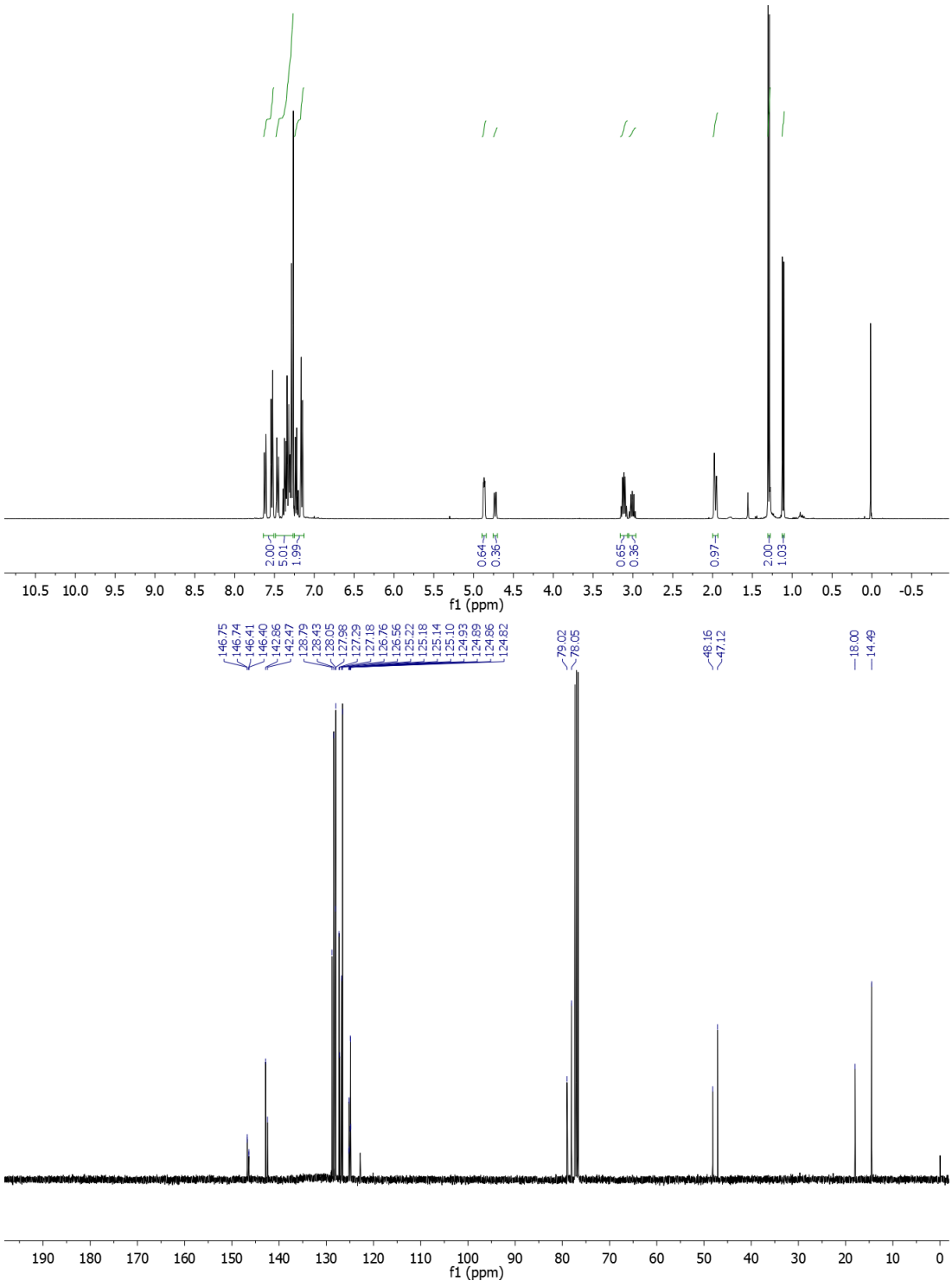
<u>*From aldehyde oxidation level:*</u> An oven-dried pressure tube equipped with a magnetic stir bar was charged with 4-(trifluoromethyl)benzyl aldehyde (34.8 mg, 0.2 mmol, 100 mol%), $RuHCl(CO)(PCy_3)_2$ (14.5 mg, 0.02 mmol, 10 mol%), and AgOTf (4.7 mg, 0.018 mmol, 9 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) and isopropyl alcohol (24 mg, 0.4 mmol, 200 mol%) were added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 30:1) to furnish the title compound (37.5 mg, 0.134 mmol, *dr*: 1.6:1) as a colorless oil (37.5 mg, *dr*: 1.6:1) in 67 % yield.

^{1}H NMR: (400 MHz, $CDCl_3$) for the 2:1 mixture of diastereomers: δ 7.57 (ddt, *J* = 34.2, 7.9, 0.8 Hz, 2H), 7.49–7.27 (m, 5H), 7.25–7.13 (m, 2H), 4.87 (dd, *J* = 5.6, 3.0 Hz, 0.64H), 4.73 (dd, *J* = 8.5, 2.2 Hz, 0.36H), 3.11 (qd, *J* = 7.0, 5.5 Hz, 0.65H), 3.01 (dq, *J* = 8.5, 7.1 Hz, 0.36H), 1.96 (ddd, *J* = 9.7, 3.0, 1.8 Hz, 1H), 1.29 (d, *J* = 7.1 Hz, 2H), 1.12 (d, *J* = 7.1 Hz, 1H).

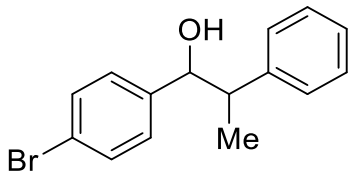
^{13}C NMR: (100 MHz, $CDCl_3$) δ 146.7 (d, *J* = 1.5 Hz), 146.4 (d, *J* = 1.5 Hz), 142.9, 142.5, 128.8, 128.4, 128.1, 128.0, 127.3, 127.2, 126.8, 126.6, 125.2 (q, *J* = 3.8 Hz), 124.9 (q, *J* = 3.7 Hz), 79.0, 78.1, 48.2, 47.1, 18.0, 14.5.

HRMS: (CI) Calcd. For $C_{16}H_{15}F_3O$ $[M+H]^+$ 281.1153, Found 281.1160.

FTIR: (neat): 3425, 2970, 1619, 1494, 1453, 1324, 1122, 1067, 1016, 841, 760, 700 cm^{-1}.


2.00
5.01
1.99
0.64
0.36
0.65
0.36
0.97
2.00
1.03
f1 (ppm)
146.75
146.74
146.41
146.40
142.86
142.47
128.79
128.43
128.05
127.98
127.29
127.18
126.76
126.56
125.22
125.18
125.14
125.10
124.93
124.89
124.86
124.82
79.02
78.05
48.16
47.12
18.00
14.49
f1 (ppm)

1-(4-bromophenyl)-2-phenylpropan-1-ol (5.3h)



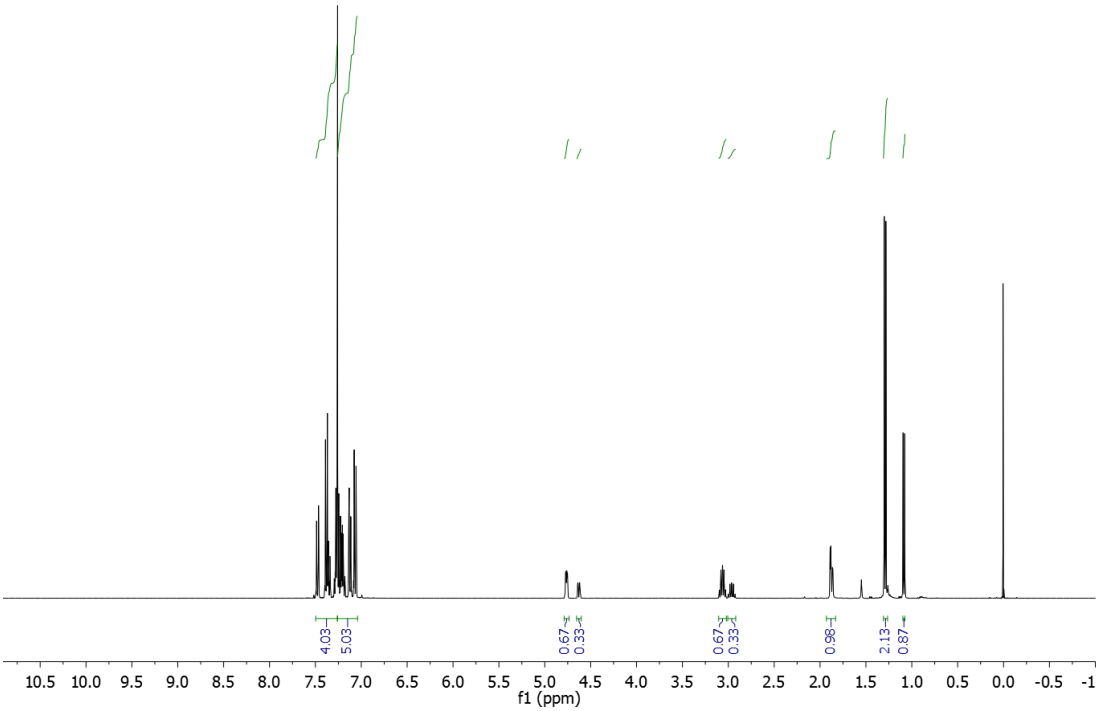
An oven-dried pressure tube equipped with a magnetic stir bar was charged with 4-bromobenzyl alcohol (37.4 mg, 0.2 mmol, 100 mol%), $RuHCl(CO)(PCy_3)_2$ (14.5 mg, 0.02 mmol, 10 mol%), and AgOTf (4.6 mg, 0.018 mmol, 9 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 30:1) to furnish the title compound (40.5 mg, 0.140 mmol, *dr*: 2:1) as a colorless oil in 70% yield.

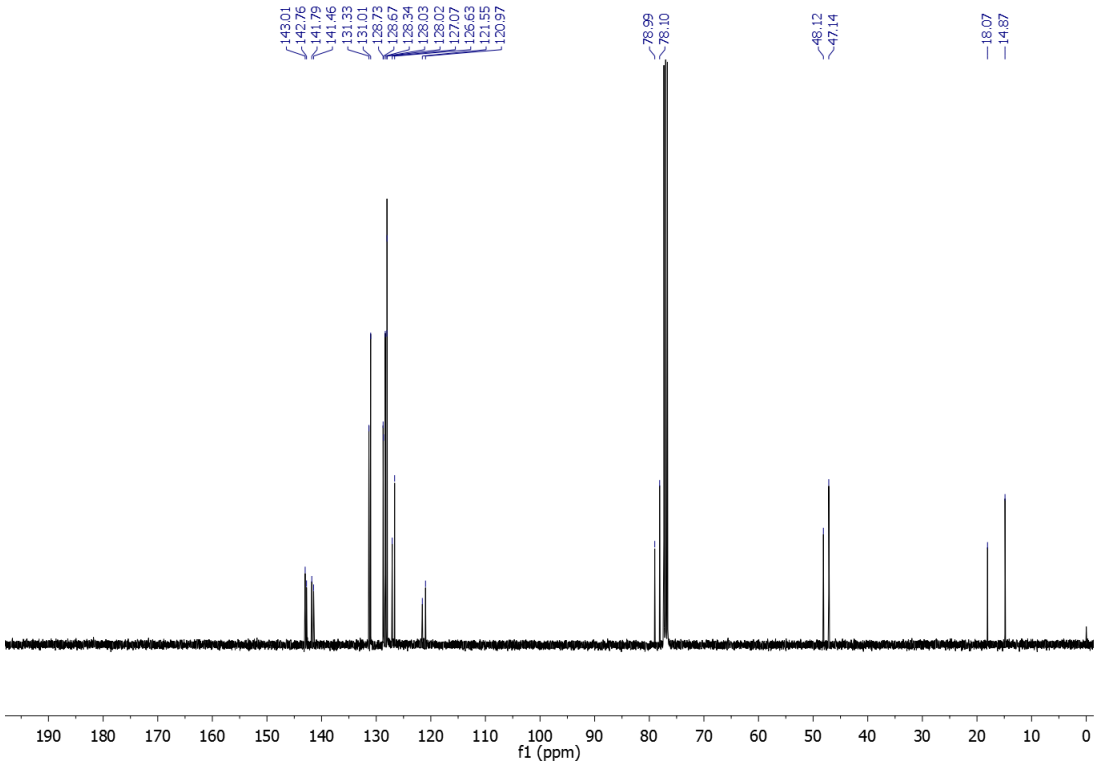
^{1}H NMR: (400 MHz, $CDCl_3$) for the 3:2 mixture of diastereomers: δ7.51–7.26 (m, 4H), 7.26–7.03 (m, 5H), 4.76 (dd, *J* = 5.9, 2.7 Hz, 0.67H), 4.63 (dd, *J* = 8.5, 2.1 Hz, 0.33H), 3.11–3.02 (m, 0.67H), 2.96 (dq, *J* = 8.5, 7.1 Hz, 0.33H), 1.87 (dd, *J* = 9.4, 2.8 Hz, 1H), 1.29 (d, *J* = 7.1 Hz, 2.13H), 1.09 (d, *J* = 7.1 Hz, 0.87H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 143.0, 142.8, 141.8, 141.5, 131.3, 131.0, 128.7, 128.7, 128.3, 128.0 (d, *J* = 1.4 Hz), 127.1, 126.6, 79.0, 78.1, 48.1, 47.1, 18.1, 14.9.

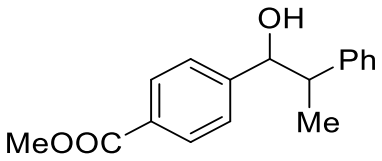
HRMS: (CI) Calcd. For $C_{15}H_{16}OBr$ $[M+H]^+$ 291.0385, Found 291.0369.

FTIR: (neat): 3411, 3026, 2964, 2927, 1592, 1486, 1452, 1403, 1183, 1070, 1024, 1008, 909, 820, 759, 699 cm^{-1}.


4.03
5.03
0.67
0.33
0.67
0.33
0.98
2.13
0.87
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


143.01
142.76
141.79
141.46
131.33
131.01
128.73
128.67
128.34
128.03
128.02
127.07
126.63
121.55
120.97
78.99
78.10
48.12
47.14
18.07
14.87
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Methyl 4-(1-hydroxy-2-phenylpropyl)benzoate (5.3i)



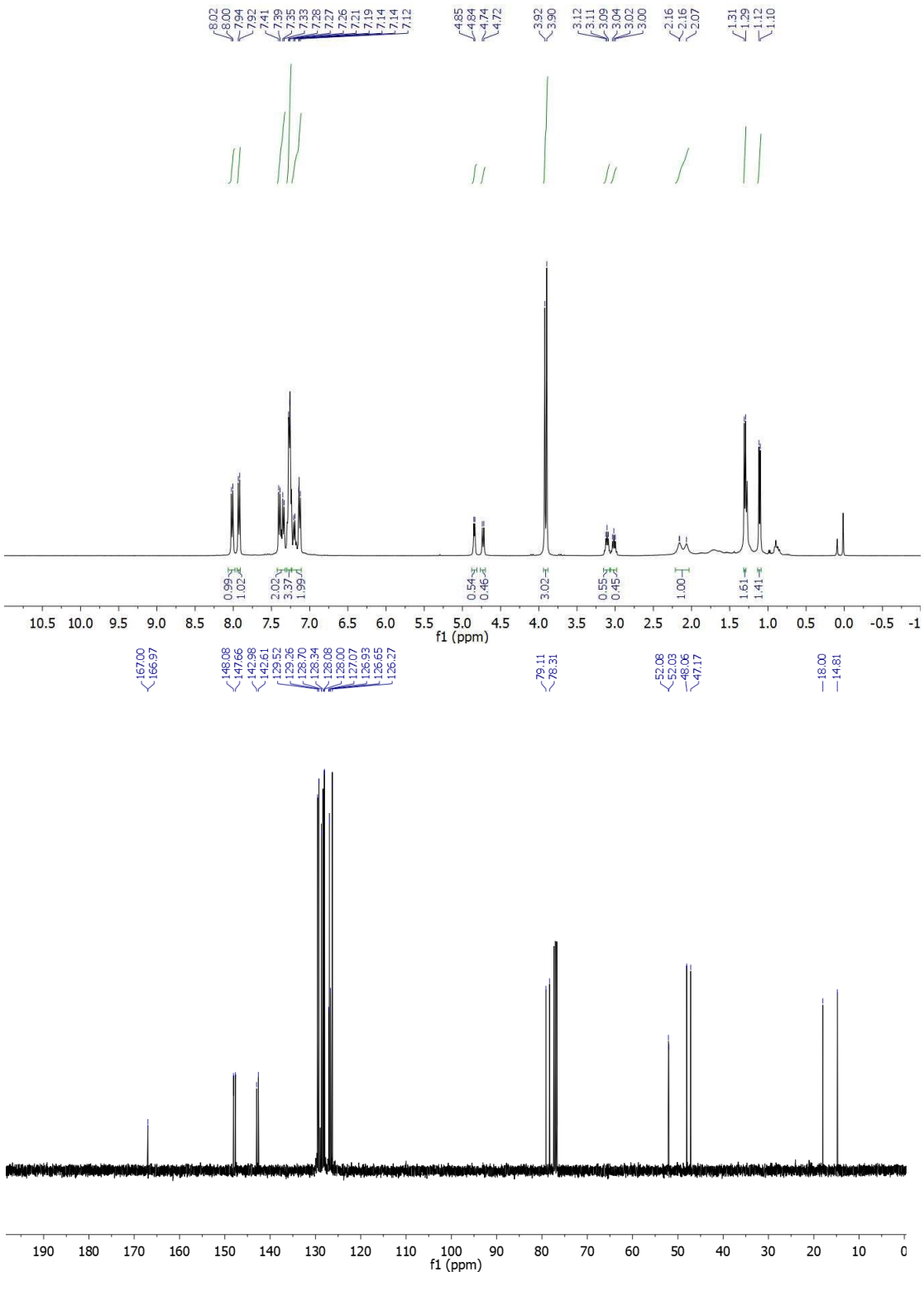
An oven-dried pressure tube equipped with a magnetic stir bar was charged with methyl 4-(hydroxymethyl)benzoate (33.2 mg, 0.2 mmol, 100 mol%), $RuHCl(CO)(PCy_3)_2$ (8.7 mg, 0.02 mmol, 6 mol%), and AgOTf (2.6 mg, 0.01 mmol, 5 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 30:1) to furnish the title compound (42.2 mg, 0.156 mmol, *dr*: 1:1) as a colorless oil in 78% yield.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.9 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 21.1, 7.6 Hz, 2H), 7.24–7.30 (m, 3H), 7.23–7.10 (m, 2H), 4.84 (d, *J* = 5.7 Hz, 0.54H), 4.73 (d, *J* = 8.2 Hz, 0.46H), 3.91 (d, *J* = 10.1 Hz, 3H), 3.21 – 3.04 (m, 0.55H), 3.02 (t, *J* = 7.4 Hz, 0.45H), 2.24–2.03 (m, 1H), 1.30 (d, *J* = 7.0 Hz, 1.6H), 1.11 (d, *J* = 7.0 Hz, 1.4H).

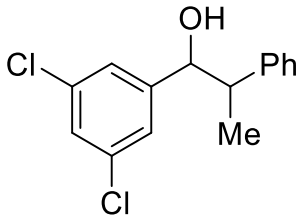
^{13}C NMR: (100 MHz, $CDCl_3$) δ 167.0 (d, *J*=2.9 Hz), 148.1, 147.7, 143.0, 142.6, 129.5, 129.3, 128.7, 128.3, 128.1, 128.0, 127.1, 126.9, 126.7, 126.3, 79.1, 78.3, 52.1 (d, *J*=5.7 Hz), 48.1, 47.2, 18.0, 14.8.

HRMS: (CI) Calcd. For $C_{17}H_{19}O_3$ $[M-H]^-$ 271.1334, Found 219.1750.

FTIR: (neat): 3468, 2926, 1717, 1610, 1494, 1435, 1277, 1177, 1109, 1018, 967, 910, 859, 771, 733, 699 cm^{-1}.


8.02
8.00
7.94
7.92
7.41
7.39
7.35
7.33
7.28
7.27
7.26
7.21
7.19
7.14
7.14
7.12
4.85
4.84
4.74
4.72
3.92
3.90
3.12
3.11
3.09
3.04
3.02
3.00
2.16
2.16
2.07
1.31
1.29
1.12
1.10
0.99
1.02
2.02
3.37
1.99
0.54
0.46
3.02
0.55
0.45
1.00
1.61
1.41
f1 (ppm)
167.00
166.97
148.08
147.66
142.98
142.61
129.52
129.26
128.70
128.34
128.08
128.00
127.07
126.93
126.65
126.27
79.11
78.31
52.08
52.03
48.06
47.17
18.00
14.81
f1 (ppm)

1-(3,5-dichlorophenyl)-2-phenylpropan-1-ol (5.3j)



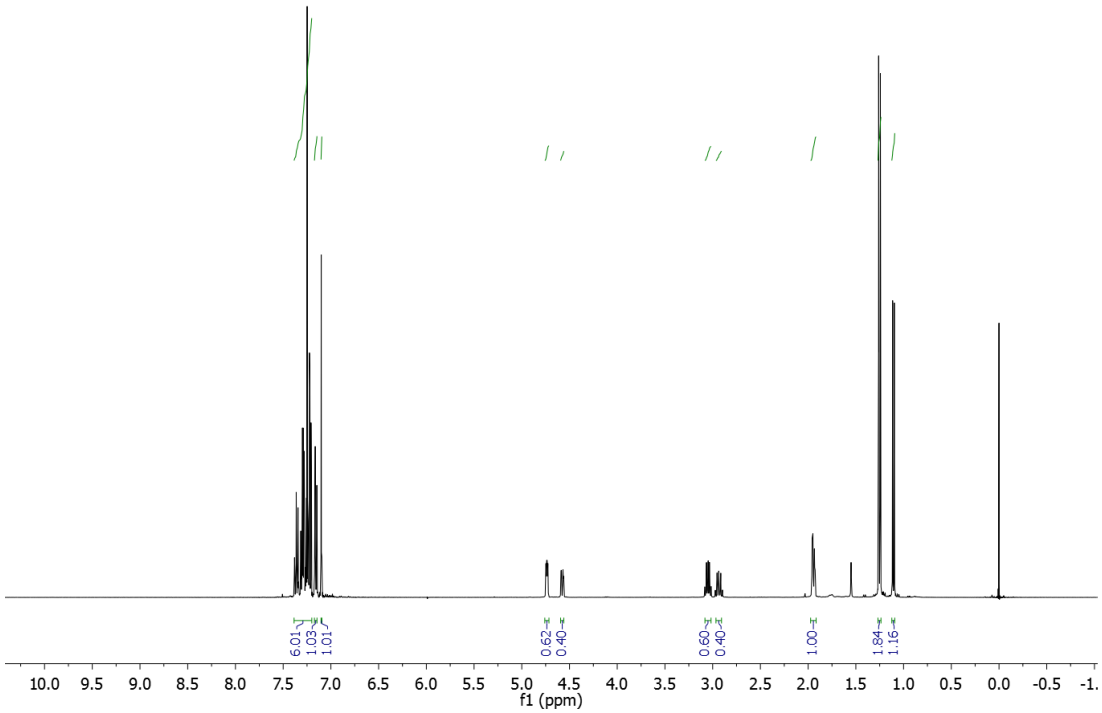
An oven-dried pressure tube equipped with a magnetic stir bar was charged with 3,5-dichlorobenzyl alcohol (35.4 mg, 0.2 mmol, 100 mol%), $RuHCl(CO)(PCy_3)_2$ (8.7 mg, 0.01 mmol, 6 mol%), and AgOTf (2.6 mg, 0.01 mmol, 5 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 30:1) to furnish the title compound (52.1 mg, 0.186 mmol, *dr*: 1.5:1) as a colorless oil in 93% yield.

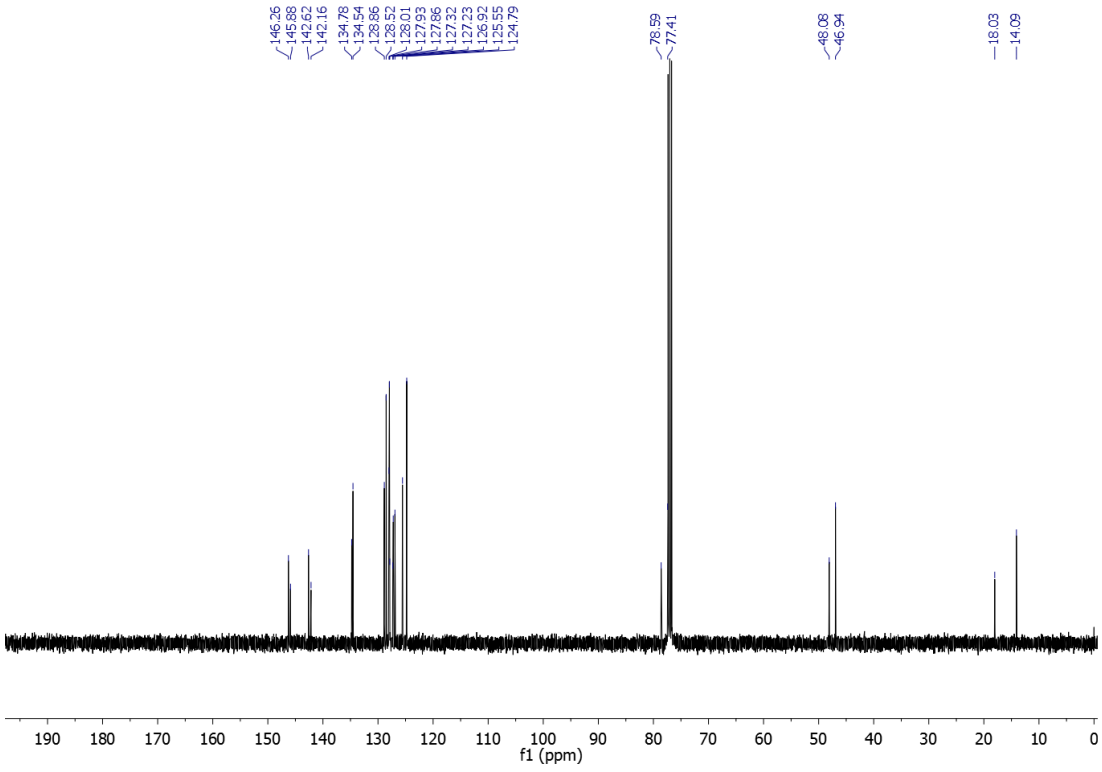
^{1}H NMR: (400 MHz, $CDCl_3$) for the 3:2 mixture of diastereomers: δ 7.40–7.21 (m, 6H), 7.19–7.15 (m, 1H), 7.11 (dd, J = 1.9, 0.7 Hz, 1H), 4.75 (dd, J = 5.3, 3.0 Hz, 0.6H), 4.59 (dd, J = 8.5, 2.2 Hz, 0.4H), 3.06 (qd, J = 7.1, 5.1 Hz, 0.6H), 2.94 (dq, J = 8.6, 7.1 Hz, 0.4H), 1.95 (dd, J = 8.9, 2.9 Hz, 2H), 1.26 (d, J = 7.1 Hz, 1.8H), 1.12 (d, J = 7.1 Hz, 1.2H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 146.3, 145.9, 142.6, 142.2, 134.8, 134.6, 128.9, 128.6, 128.0, 127.9, 127.9, 127.3, 127.2, 126.9, 125.6, 124.8, 78.6, 77.4, 48.1, 46.9, 18.0, 14.1.

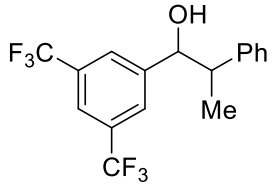
HRMS: (ESI) Calcd. For $C_{15}H_{14}Cl_2OAg$ $[M+Ag]^+$: 386.9467, Found, 386.9467.

FTIR: (neat): 3424, 3082, 3028, 2974, 1588, 1567, 1494, 1452, 1432, 1380, 1200, 1063, 1008, 857, 797, 699 cm^{-1}.


6.01
1.03
1.01
0.62
0.40
0.60
0.40
1.00
1.84
1.16
f1 (ppm)


146.26
145.88
142.62
142.16
134.78
134.54
128.86
128.52
128.01
127.93
127.86
127.32
127.23
126.92
125.55
124.79
78.59
77.41
48.08
46.94
18.03
14.09
f1 (ppm)

1-(3,5-bis(trifluoromethyl)phenyl)-2-phenylpropan-1-ol (5.3k)



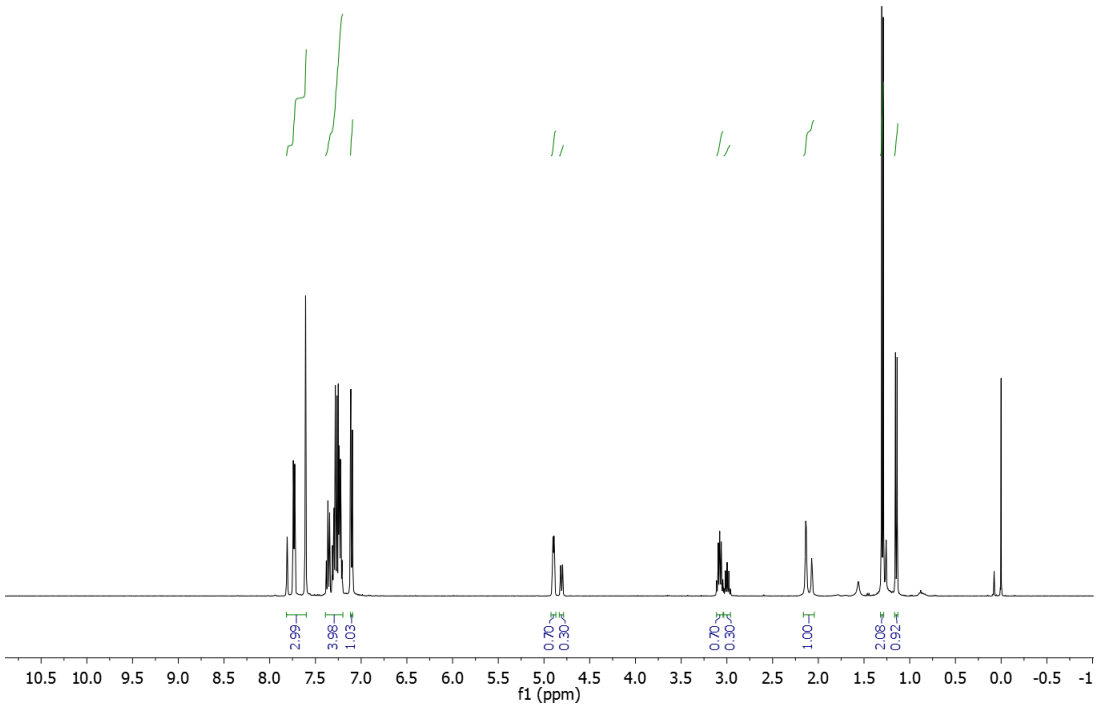
An oven-dried pressure tube equipped with a magnetic stir bar was charged with (3,5-bis(trifluoromethyl)phenyl)methanol (48.8 mg, 0.2 mmol, 100 mol%), $RuHCl(CO)(PCy_3)_2$ (8.7 mg, 0.01 mmol, 6 mol%), and AgOTf (2.6 mg, 0.01 mmol, 5 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 30:1) to furnish the title compound (50.2 mg, 0.144 mmol, *dr*: 2.2:1) as a colorless oil in 72% yield.

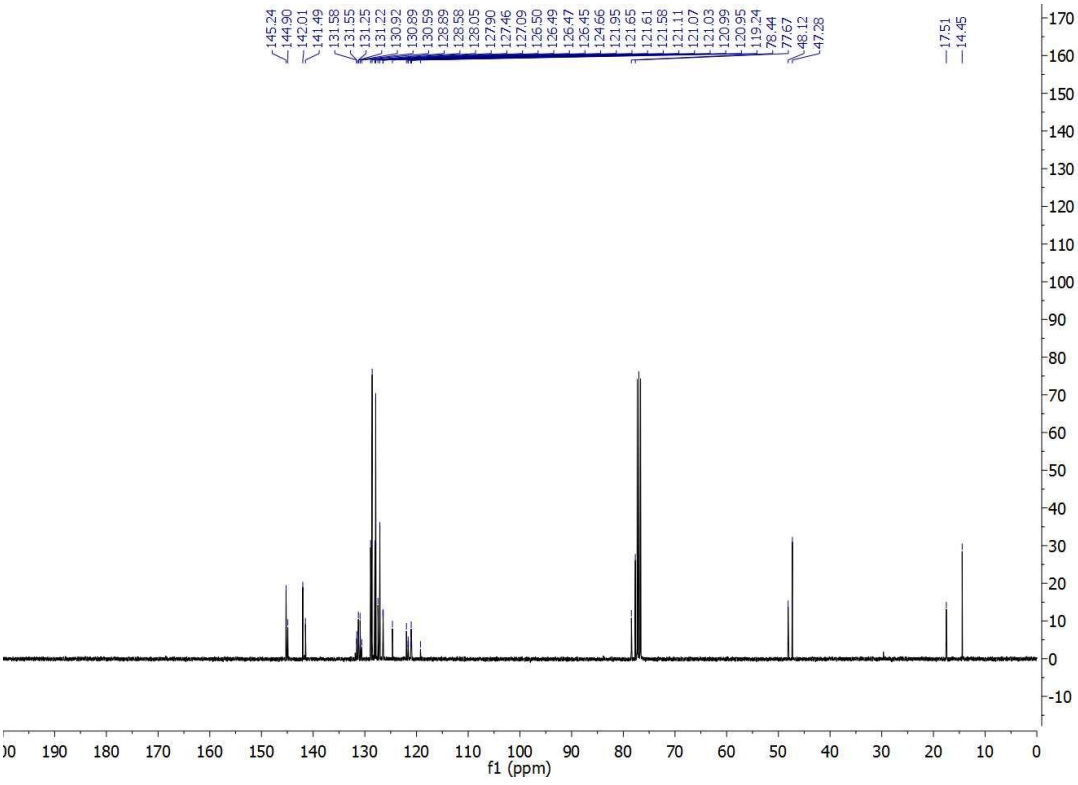
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.55 (m, 3H), 7.41–7.19 (m, 4H), 7.12–7.09 (m, 1H), 4.90 (dd, *J* = 5.8, 2.2 Hz, 0.7H), 4.83–4.79 (m, 0.3H), 3.13–3.04 (m, 0.7H), 3.00 (p, *J* = 7.2 Hz, 0.3H), 2.10 (dd, *J* = 25.7, 2.9 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 2.08H), 1.15 (d, *J* = 7.1 Hz, 0.92H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 145.2, 144.9, 142.0, 141.5, 131.6 (d, *J* = 3.5 Hz), 131.2 (d, *J* = 3.5 Hz), 130.9 (d, *J* = 3.7 Hz), 130.6, 128.89, 128.6, 128.1, 127.9, 127.5, 127.1, 126.5, 126.5, 126.4, 126.4, 124.7, 121.6 (t, *J* = 3.8 Hz), 121.0 (p, *J* = 3.9 Hz), 119.2, 78.4, 77.7, 48.1, 47.3, 17.5, 14.5.

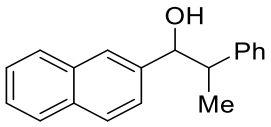
HRMS: (CI) Calcd. For $C_{17}H_{13}F_6O$ $[M-H]^+$: 347.0871, Found, 347.0868.

FTIR: (neat): 3458, 2967, 1624, 1495, 1453, 1365, 1275, 1168, 1126, 1024, 1009, 899, 874, 842, 761, 700, 681 cm^{-1}.


2.99
3.98
1.03
0.70
0.30
0.70
0.30
1.00
2.08
0.92
f1 (ppm)


145.24
144.90
142.01
141.49
131.58
131.55
131.25
131.22
130.92
130.89
130.59
128.89
128.58
128.05
127.90
127.46
127.09
126.50
126.49
126.47
126.45
124.66
121.95
121.65
121.61
121.58
121.11
121.07
121.03
120.99
120.95
119.24
78.44
77.67
48.12
47.28
17.51
14.45
f1 (ppm)

1-(naphthalen-2-yl)-2-phenylethan-1-ol (5.3l)



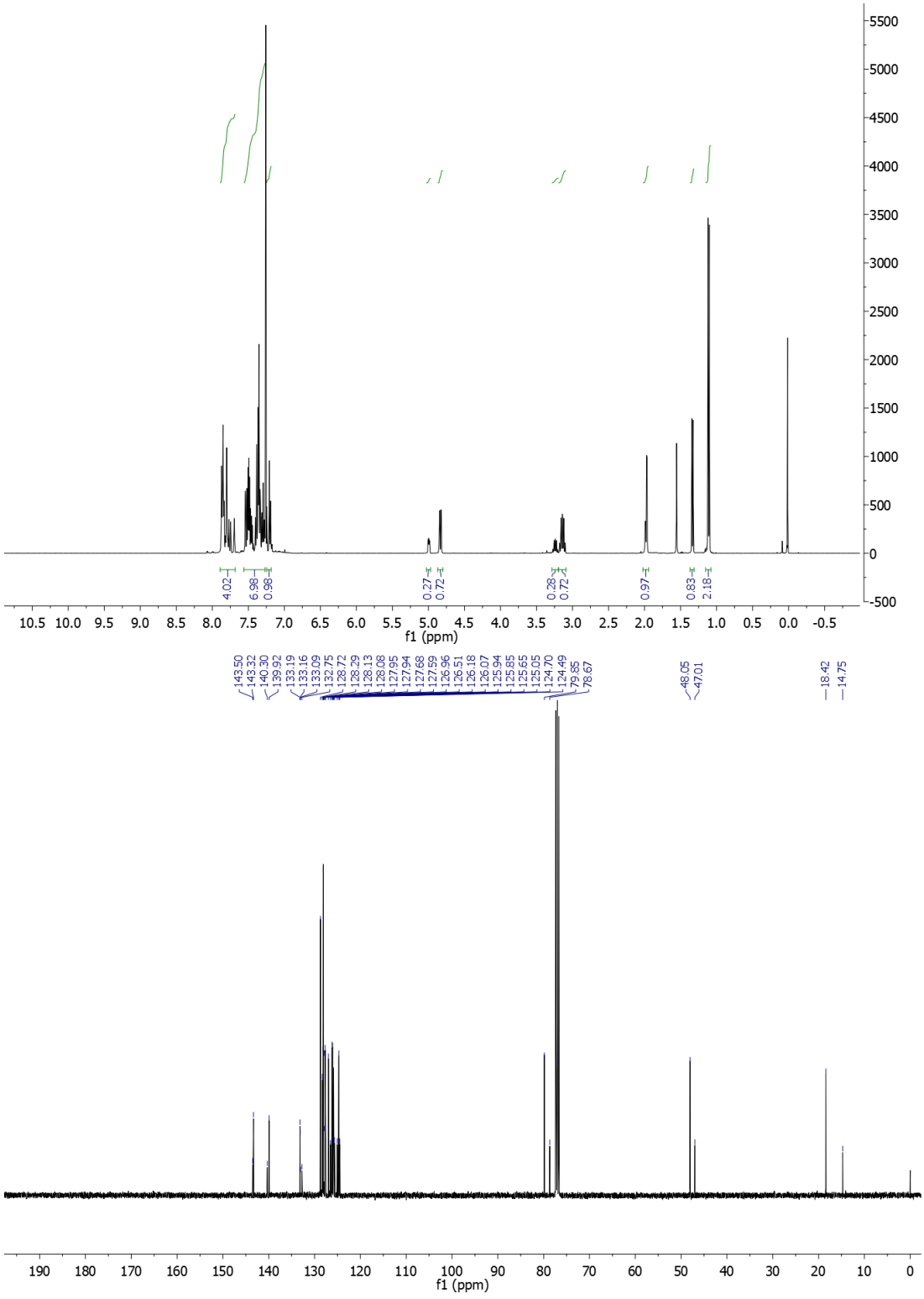
An oven-dried pressure tube equipped with a magnetic stir bar was charged with naphthalen-2-ylmethanol (31.6 mg, 0.2 mmol, 100 mol%), $RuHCl(CO)(PCy_3)_2$ (14.5 mg, 0.02 mmol, 10 mol%), and AgOTf (4.6 mg, 0.018 mmol, 9 mol%). The reaction vessel was placed under an atmosphere of argon. Styrene (0.2 mL, 1 M, 870 mol%) was added by syringe. The reaction vessel was sealed and the reaction mixture was allowed to stir at 100 ˚C for 24 h. The reaction was allowed to reach ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2: hexanes:ethyl acetate, 30:1) to furnish the title compound (31.5 mg, 0.120 mmol, *dr*: 2.3:1) as a colorless oil in 60% yield.

^{1}H NMR: (400 MHz, $CDCl_3$) for the 2.6:1 mixture of diastereomers: δ 7.90–7.68 (m, 4H), 7.57–7.27 (m, 7H), 7.25–7.18 (m, 1H), 5.00 (dd, *J* = 5.6, 3.1 Hz, 0.27H), 4.84 (dd, *J* = 8.8, 2.2 Hz, 0.72H), 3.24 (qd, *J* = 7.0, 5.4 Hz, 0.28H), 3.14 (dq, *J* = 8.8, 7.1 Hz, 0.72H), 1.98 (dd, *J* = 7.8, 2.9 Hz, 1H), 1.33 (d, *J* = 7.0 Hz, 0.83H), 1.11 (d, *J* = 7.1 Hz, 2.18H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 143.5, 143.3, 140.3, 139.9, 133.2 (d, *J* = 2.3 Hz), 133.1, 132.8, 128.7, 128.3, 128.1, 128.1, 128.0 (d, *J* = 1.5 Hz), 127.7, 127.6, 127.0, 126.5, 126.2, 126.1, 125.9, 125.9, 125.7, 125.1, 124.7, 124.5, 79.9, 78.7, 48.1, 47.0, 18.4, 14.8.

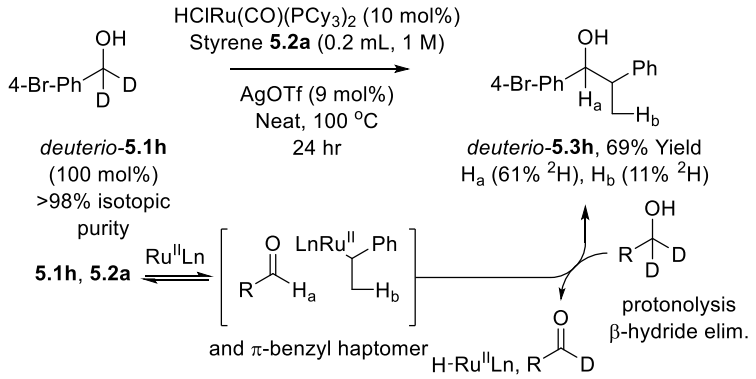
HRMS: (CI) Calcd. For $C_{19}H_{18}O$ $[M]^+$ 262.1358, Found 262.1354.

FTIR: (neat): 3414, 3056, 3026, 2964, 2925, 1601, 1493, 1451, 1374, 1269, 1164, 1091, 1022, 1008, 891, 856, 799, 747, 699, 666 cm^{-1}.


4.02
6.98
0.98
0.27
0.72
0.28
0.72
0.97
0.83
2.18
f1 (ppm)
143.50
143.32
140.30
139.92
133.19
133.16
133.09
132.75
128.72
128.29
128.13
128.08
127.95
127.94
127.68
127.59
126.96
126.51
126.18
126.07
125.94
125.85
125.65
125.05
124.70
124.49
79.85
78.67
48.05
47.01
18.42
14.75
f1 (ppm)

Isotopic Labelling Studies:

Deuterium labelling studies of 5.1h:



^{1}H NMR: (400 MHz, $CDCl_3$) for the 1.5:1 mixture of diastereomers: δ 7.51–7.26 (m, 4H), 7.25–7.02 (m, 5H), 4.75 (dd, *J*=5.8, 3.3 Hz, 0.22H), 4.62 (dd, *J*=8.5, 2.4 Hz, 0.17H), 3.05 (q, *J*=7.0 Hz, 0.59H), 3.00–2.90 (m, 0.40H), 1.99–1.80 (m, 1H), 1.28 (d, *J*=7.1 Hz, 1.72H), 1.08 (d, *J*=7.0 Hz, 1.17H).

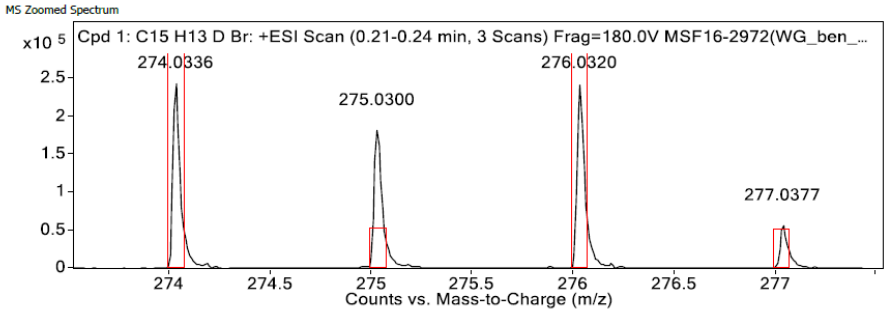
^{2}H NMR: (77 MHz, $CDCl_3$) for the 1.5:1 mixture of diastereomers: δ 4.69 (d, *J*=9.5 Hz, 0.61H), 1.20 (d, *J*=15.8 Hz, 0.11H).

HRMS: (ESI): Calcd. For $C_{15}H_{12}DBr$ $[M\text{-}OH]^+$ 274.0336, Found 274.0336.

Target Compound Screening Report

Data File	MSF16-2972(WG_ben_Ha_and_Hb)_hrESIpos1.d	**Sample Name**	2972(WG_ben_Ha_and_Hb)	**Comment**	2972(WG_ben_Ha_and_Hb)
Position	P1-B2	**Instrument Name**	Instrument 1	**User Name**	
Acq Method	pos.m	**Acquired Time**	8/16/2016 10:42:26 AM	**DA Method**	KS.m

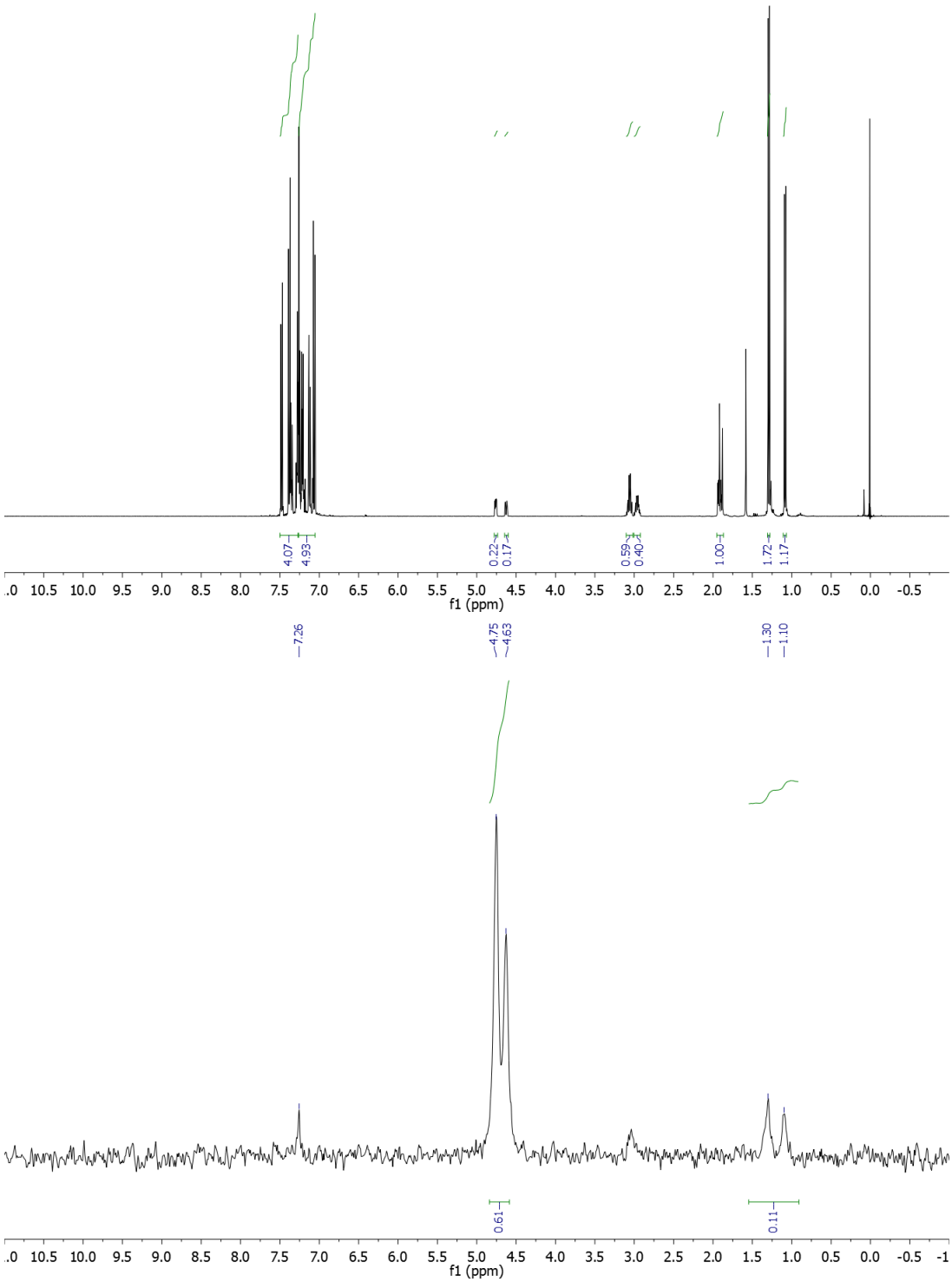
MS Zoomed Spectrum



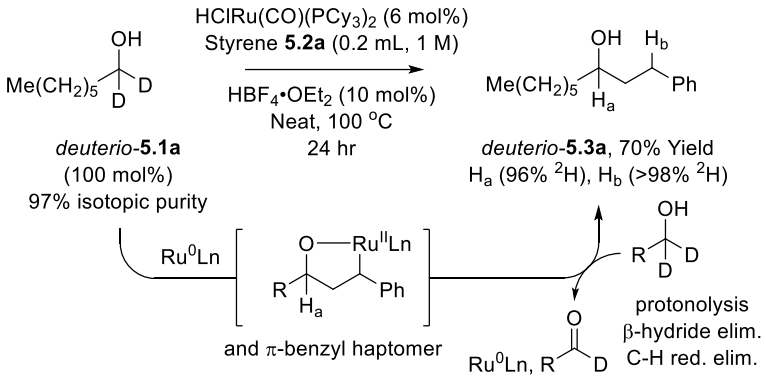
MS Spectrum Peak List

Obs. m/z	Calc. m/z	Charge	Abund	Formula	Ion/Isotope	Tgt Mass Error (ppm)
274.03360	274.03360	1	244199.59	C15H13DBr	M+	0.06
275.03000	275.03700	1	182693.41	C15H13DBr	M+	25.45
276.03200	276.03170	1	242491.56	C15H13DBr	M+	-1.12
277.03770	277.03500	1	56898.75	C15H13DBr	M+	-9.7
278.04280	278.03840	1	8108.76	C15H13DBr	M+	-16.15
279.04870	279.04170	1	3618.56	C15H13DBr	M+	-24.94
297.23500			458616.28			

--- End Of Report ---


4.07
4.93
0.22
0.17
0.59
0.40
1.00
1.72
1.17
f1 (ppm)
7.26
4.75
4.63
1.30
1.10
0.61
0.11
f1 (ppm)

Deuterium labelling studies of 5.1a:



^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 2H), 7.23–7.15 (m, 3H), 3.63 (s, 0.03H), 2.82–2.73 (m, 0.2H), 2.73–2.57 (m, 0.8H), 1.75 (qd, *J* = 13.8, 8.1 Hz, 2H), 1.51–1.22 (m, 11H), 0.92–0.83 (m, 3H).

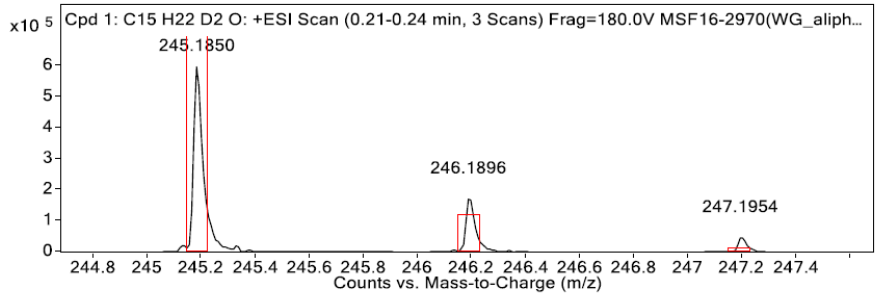
^{2}H NMR: (77 MHz, $CDCl_3$) δ 3.62 (s, 1H), 2.79 (s, 1H).

HRMS: (ESI): Calcd. For $C_{15}H_{22}D_2O$ $[M+Na]^+$ 245.1845, Found 245.1850.

Target Compound Screening Report

Data File	MSF16-2970(WG_aliph_Ha_and_Hb)_hrESIpos1.d	**Sample Name**	2970(WG_aliph_Ha_and_Hb)	**Comment**	2970(WG_aliph_Ha_and_Hb)
Position	P1-B1	**Instrument Name**	Instrument 1	**User Name**	
Acq Method	pos.m	**Acquired Time**	8/16/2016 10:41:32 AM	**DA Method**	KS.m

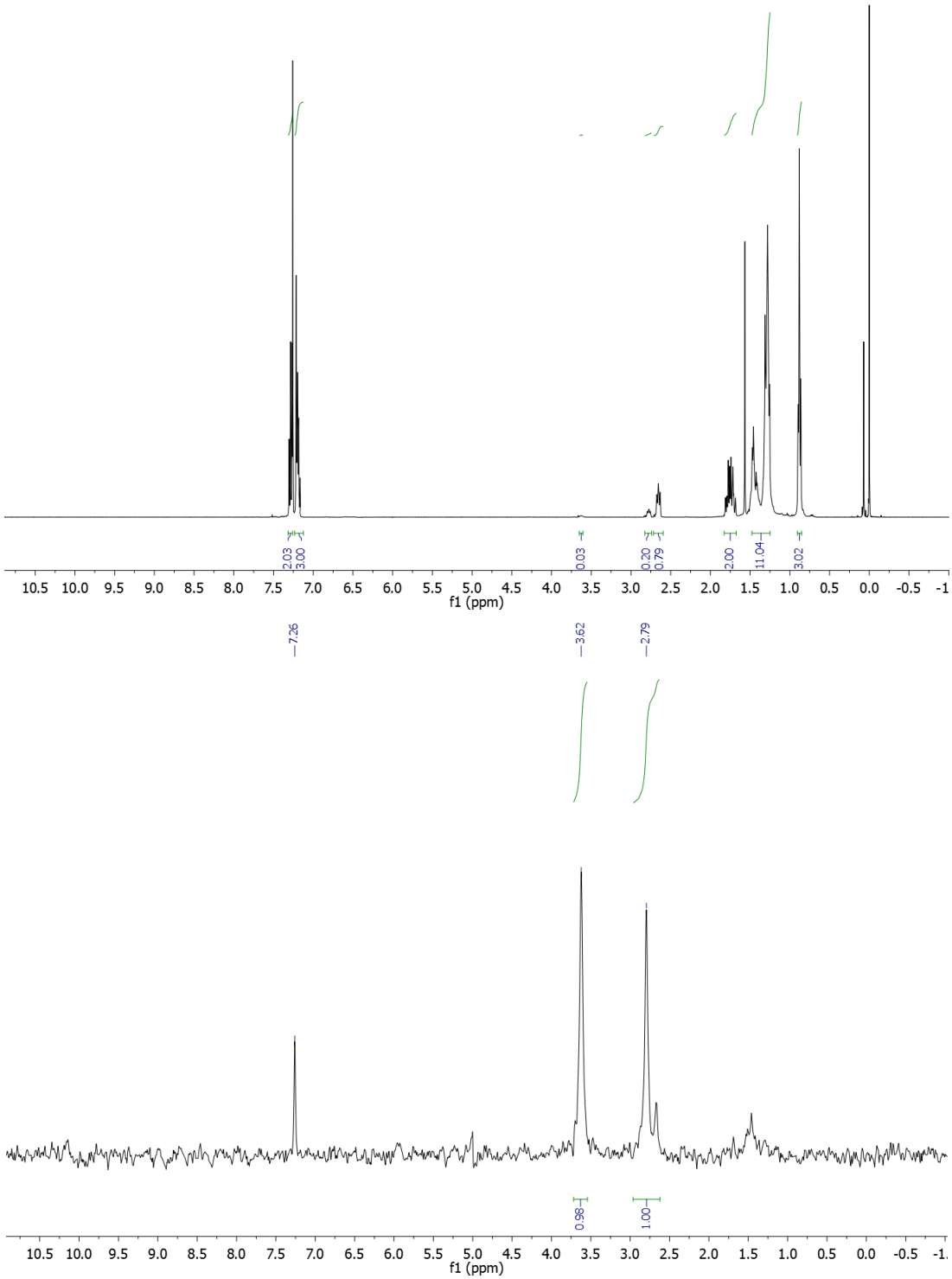
MS Zoomed Spectrum



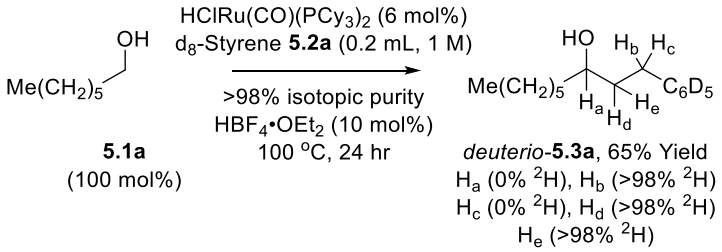
MS Spectrum Peak List

Obs. m/z	Calc. m/z	Charge	Abund	Formula	Ion/Isotope	Tgt Mass Error (ppm)
245.18500	245.18450	1	604815.1	C15H22D2O	(M+Na)+	2.07
246.18960	246.18790	1	180698.37	C15H22D2O	(M+Na)+	6.89
261.14950		1	116558.7			
307.15560		1	415395.29			
308.16010		1	127644.09			
323.12850		1	89002.26			
419.31590		1	98135.17			
441.29830		1	482678.6			
442.30110		1	126728.54			
457.27570		1	139965.61			

--- End Of Report ---


2.03
3.00
0.03
0.20
0.79
2.00
11.04
3.02
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)
7.26
3.62
2.79
0.98
1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)

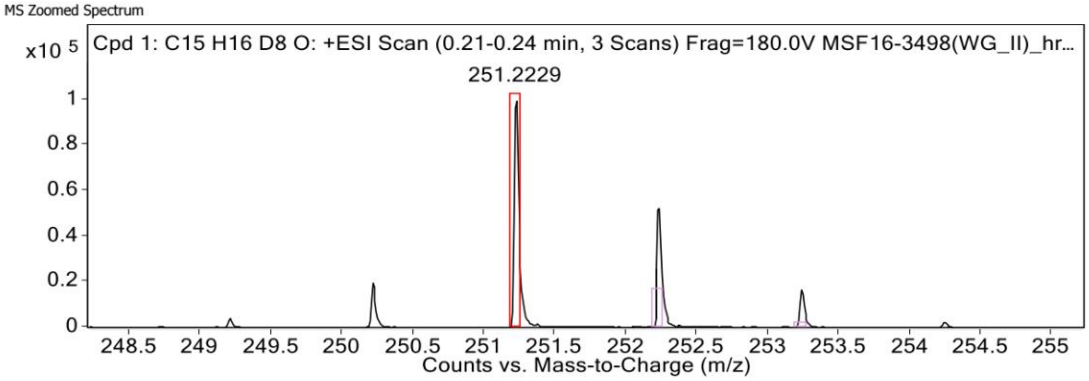
Deuterium labelling studies of 5.1a with d_8-Styrene:



^{1}H NMR: (400 MHz, $CDCl_3$): δ 3.61 (s, 1H), 2.76 (s, 0.79H), 2.65 (d, *J*=13.4 Hz, 0.21H), 1.52–1.17 (m, 11H), 0.95–0.82 (m, 3H).

^{2}H NMR: (92 MHz, CH_2Cl_2): δ 7.30 (d, *J*=7.3 Hz, 5H), 2.73 (d, *J*=11.0 Hz, 1H), 1.75 (d, *J*=5.1 Hz, 2H).

HRMS: (ESI): Calcd. For $C_{15}H_{16}D_8NaO$ $[M+Na]^+$ 251.2222, Found 251.2229.



MS Spectrum Peak List

Obs. m/z	Calc. m/z	Charge	Abund	Formula	Ion/Isotope	Tgt Mass Error (ppm)
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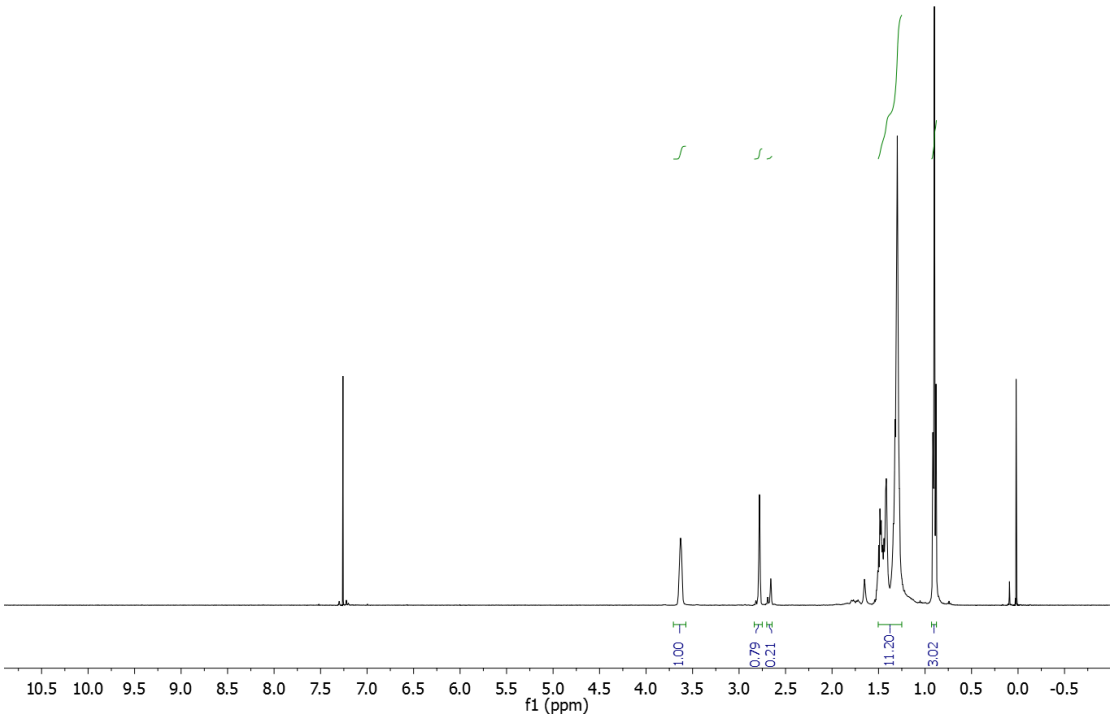
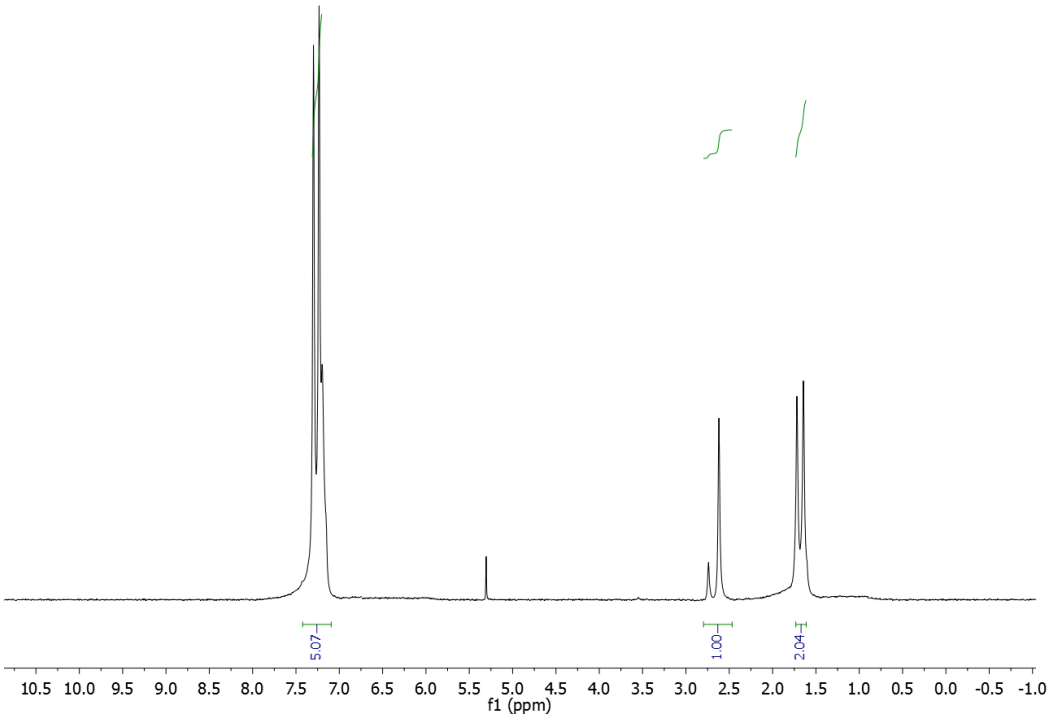
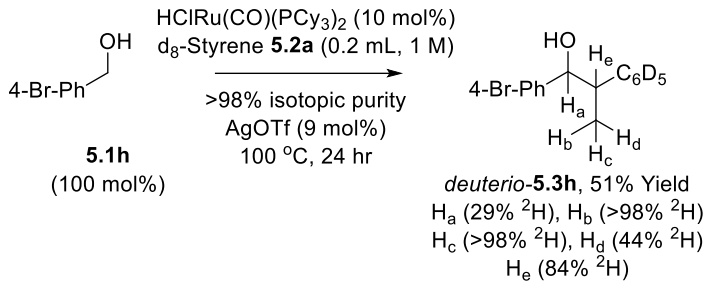
297.23520			163056.72			

--- End Of Report ---


1.00
0.79
0.21
11.20
3.02
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


5.07
1.00
2.04
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

Deuterium labelling studies of 5.1h with d_8-Styrene:



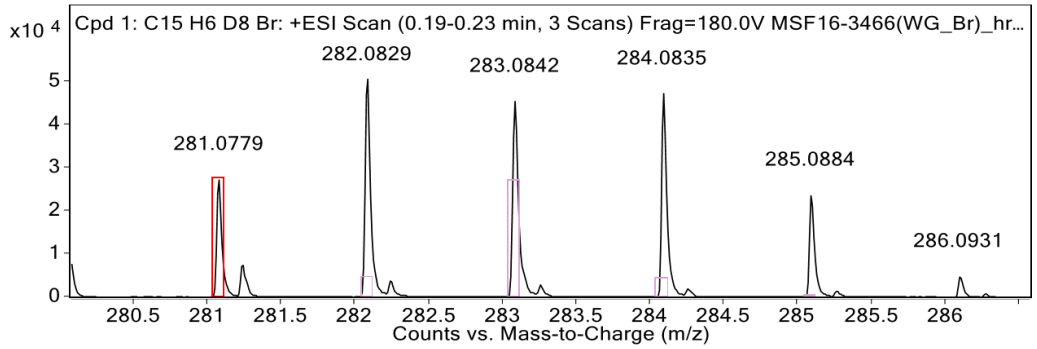
Spectrum of *deuterio*-5.3h

^{1}H NMR: (400 MHz, $CDCl_3$) for the 1:1 mixture of diastereomers: δ 7.48–7.43 (m, 1H), 7.39–7.33 (m, 1H), 7.21–7.15 (m, 1H), 7.05–7.01 (m, 1H), 4.65 (dd, *J*=47.5, 2.9 Hz, 0.56H), 2.97 (dd, *J*=34.9, 5.6 Hz, 0.15H), 2.12–1.81 (m, 1H), 1.38–0.96 (m, 0.73H).

^{2}H NMR: (92 MHz, CH_2Cl_2) for the 1:1 mixture of diastereomers: δ 7.27 (dd, *J*=13.1, 6.4 Hz, 5H), 4.68 (d, *J*=9.6 Hz, 0.44H), 2.98 (d, *J*=7.8 Hz, 0.84H), 1.15 (dd, *J*=19.4, 1.7 Hz, 2.29H).

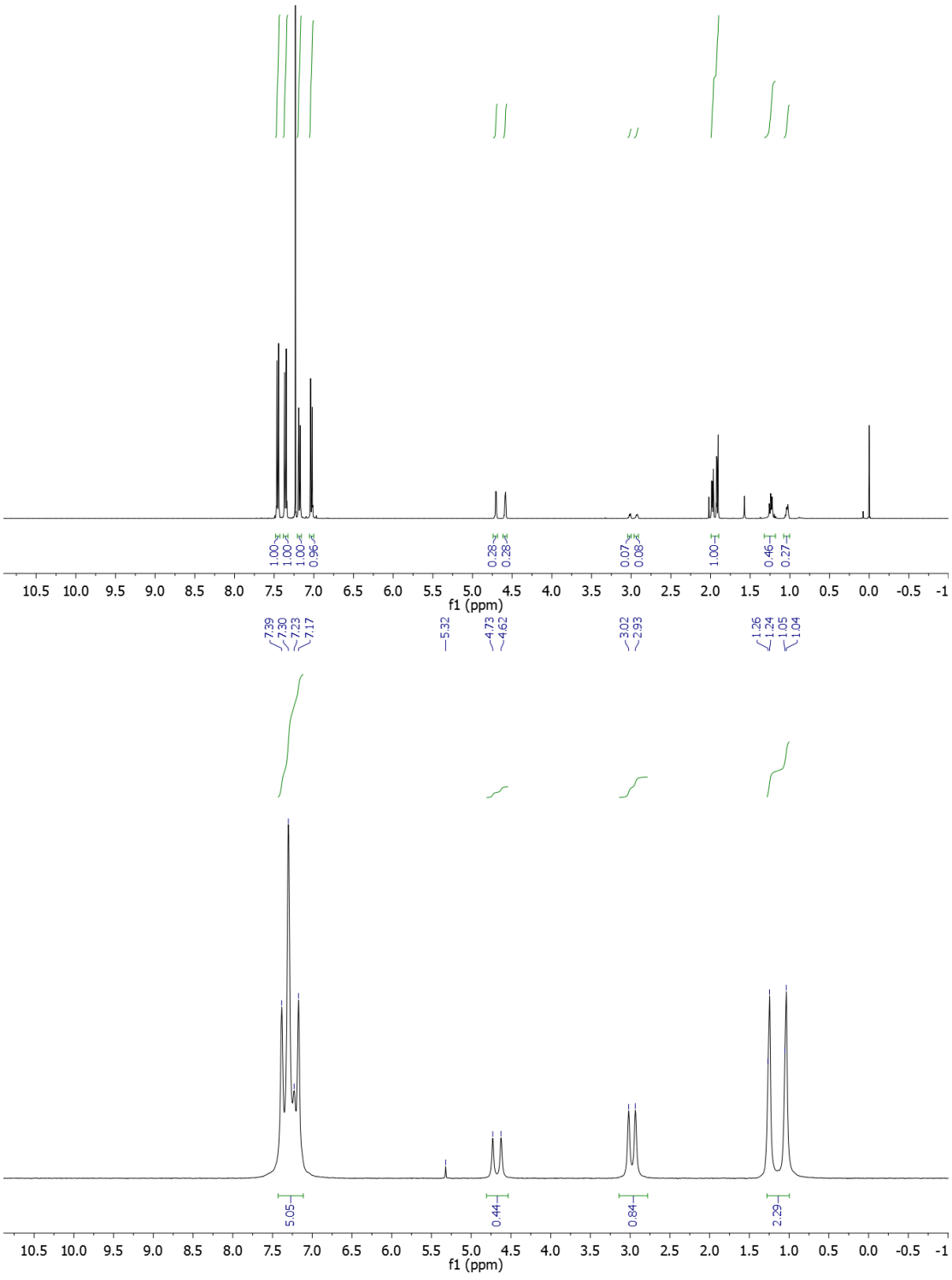
HRMS: (ESI): Calcd. For $C_{15}H_6D_8Br$ $[M\text{-}OH]^+$ 281.0776, Found 281.0779.

MS Zoomed Spectrum



MS Spectrum Peak List

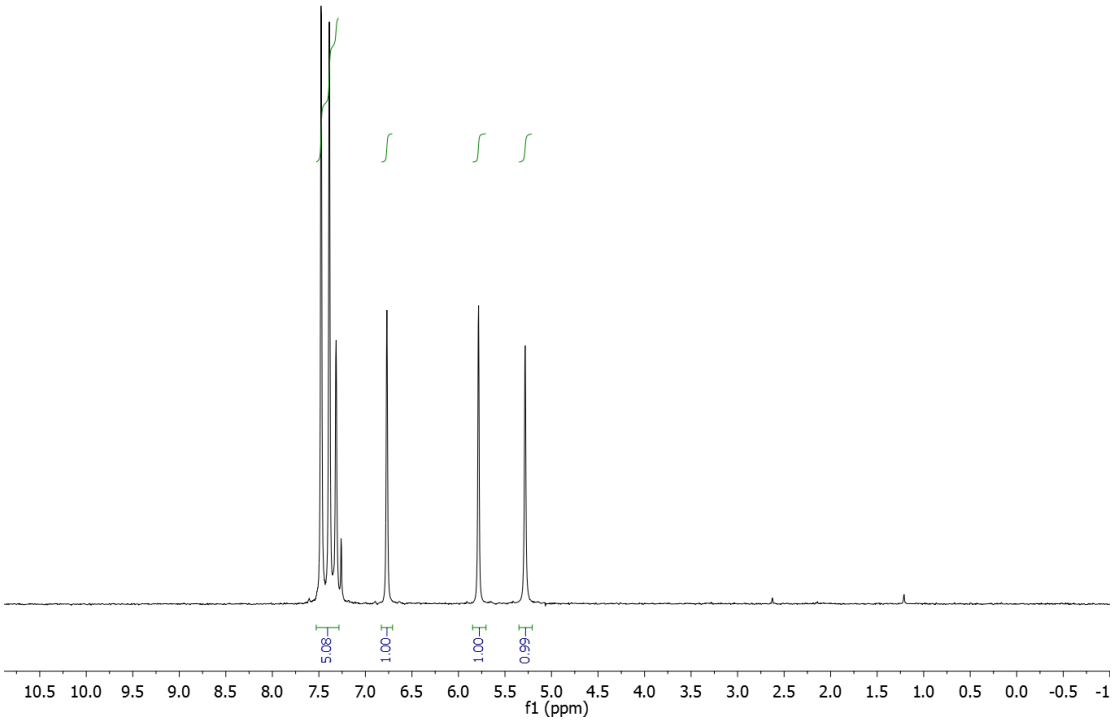
Obs. m/z	Calc. m/z	Charge	Abund	Formula	Ion/Isotope	Tgt Mass Error (ppm)
281.07790	281.07760		27498.22	C15H6D8Br	M+	1.37
282.08290			51298.98			
283.08420			45451.28			
284.08350			47169.41			
285.08840		1	24156.47			
297.23550		1	21168.97			
322.07550			15316.43			
323.07640			13439.55			
324.07590			14006.07			
441.29900		1	15010.25			


1.00
1.00
1.00
0.96
0.28
0.28
0.07
0.08
1.00
0.46
0.27
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)
7.39
7.30
7.23
7.17
5.32
4.73
4.62
3.02
2.93
1.26
1.24
1.05
1.04
5.05
0.44
0.84
2.29
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

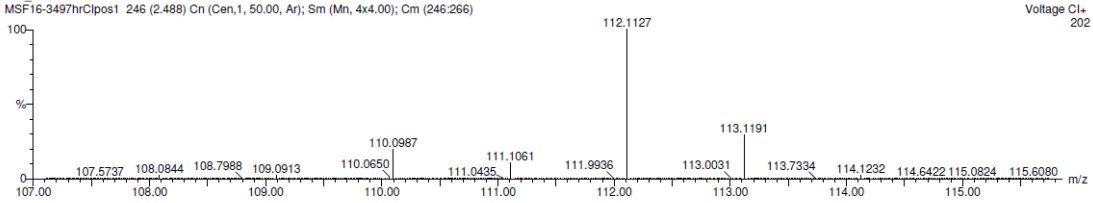
Spectrum of recovered styrene

^{2}H NMR: (92 MHz, $CHCl_3$) δ 7.64–7.27 (m, 5H), 6.77 (s, 1H), 5.78 (s, 1H), 5.28 (s, 1H).

HRMS: (CI): Calcd. For C_8D_8 M^+ 112.1128, Found 112.1127.



Monoisotopic Mass, Odd and Even Electron Ions
151 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 1H: 0-100 2H: 6-8
WG_IV
MSF16-3497hrClpos1 246 (2.488) Cn (Cen,1, 50.00, Ar); Sm (Mn, 4x4.00); Cm (246:266)
Voltage CI+ 202



Minimum:	15.00				-1.5		
Maximum:	100.00		5.0	10.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
110.0987	19.25	110.0987	0.0	0.0	5.5	225786.8	C8 2H7
112.1127	100.00	112.1128	-0.1	-0.9	5.0	1628386.4	C8 2H8

Appendix

List of Abbreviations and Acronyms

PG	protecting group
DMB	2,4-dimethoxybenzyl
Cbz	carboxybenzyl
Dba	dibenzylideneacetone
9-BBN	9-borabicyclo[3.3.1]nonane
ee	enantiomeric excess
dr	diastereomeric ratio
acac	acetylacetonate
DCE	1,2-dichloroethane
HMDS	bis(trimethylsilyl)amide
cod	1,4-cyclooctadiene
LLS	longest linear steps

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Chapter 1

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